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A 10-YEAR FOLLOW-UP OF PEOPLE WITH MULTIPLE SCLEROSIS - ASPECTS OF DISABILITY AND HEALTH, USE OF AND SATISFACTION WITH CARE, AND FEASIBILITY OF COGNITIVE BEHAVIOURAL THERAPY

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A 10-YEAR FOLLOW-UP OF PEOPLE WITH MULTIPLE SCLEROSIS - ASPECTS OF DISABILITY AND HEALTH, USE OF AND SATISFACTION WITH CARE, AND FEASIBILITY OF COGNITIVE BEHAVIOURAL THERAPY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background: Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease in the central nervous system which affects a number of life areas of the afflicted individual. Detailed knowledge is required on functioning and health in people with MS (PwMS) from a broad and longitudinal perspective. There is also an urgent need to increase knowledge about effective methods for alleviating depressive symptoms in PwMS. **Aims:** The overall aim in this thesis was to explore the occurrence of disability, health related quality of life (HRQL), use of care and patient satisfaction with care, and to explore the importance of different variables to predict the occurrence of disability, HRQL and use of care in PwMS in a long-term longitudinal perspective. In addition, the aim was to evaluate the feasibility of face-to -face cognitive behavioural therapy (CBT) for alleviating depressive symptoms in PwMS. **Material and Methods:** Study I, II and III were based on a 10-year follow-up of a population-based sample of PwMS in Stockholm County (n=166). A total of 123 PwMS agreed to participate in the 10-year follow-up. Information on disease-specific variables, contextual factors, various aspects of disability, HRQL and patient satisfaction with care were collected by home visits at baseline and at the 10-year follow-up. Information regarding time and cause of death was collected from the National Board of Health and Welfare. Information regarding use of care was collected from the Stockholm County Council. Recruitment of patients to study IV (n=15) was conducted at the Department of Neurology, Karolinska University Hospital. Inclusion criteria were a definite and informed MS-diagnosis and sub-threshold to moderate depressive symptoms. The intervention included 15-20 individual sessions with a licensed psychotherapist. Main outcome was feasibility of methods and measurements used and depressive symptoms. Follow-ups were conducted three weeks and three months after completed intervention. **Results:** There was no change in occurrence of PwMS with cognitive impairment, depressive symptoms or restrictions in social/lifestyle activities from baseline to the 10-year follow-up. There was an increase in occurrence of PwMS with limitation in manual dexterity, walking ability and activities of daily living over time. Overall, HRQL was quite stable over time. The use of care over time was extensive, including primary care, hospital outpatient and inpatient care. Higher disease severity was an important variable in predicting disability. Low coping capacity, depressive symptoms and cognitive impairment were important variables in predicting HRQL. Low coping capacity, manual dexterity and progress in disease severity were important variables in predicting the use of care. Satisfaction with care was quite stable over time. Overall, the methods and measurements used in the pilot feasibility study of face-to-face CBT were found to be feasible. **Conclusion:** Awareness of the psychological aspects of the disease needs to increase among care professionals. There is a potential to decrease the impact of modifiable factors on HRQL in PwMS as well as meeting the need for environmental facilitators aiming at reducing disability. By establishing the PwMS as full partners to their care providers in care decisions and implement strategies to coordinate care between care providers there is a potential to increase efficacy/outcome of care. Face-to-face CBT is feasible for use in PwMS.

SAMMANFATTNING

Bakgrund: Multipel skleros (MS) är en neuroinflammatorisk och neurodegenerativ sjukdom i det centrala nervsystemet som påverkar livet för den drabbade personen på flera sätt. Detaljerad kunskap om funktion och hälsa hos personer med MS (PmMS) i ett långtidsperspektiv behövs. Det behövs också mer kunskap om effektiva metoder för att minska depressiva symtom hos PmMS. **Syfte:** Det övergripande syftet med avhandlingen var att undersöka förekomst av funktionshinder, hälsorelaterad livskvalitet (HRLK), utnyttjande av och tillfredställelse med sjukvård, samt att undersöka betydelsen av olika faktorer för att predicera förekomst av funktionshinder, HRLK och utnyttjande av vård hos PmMS i ett långtidsperspektiv. Ytterligare ett syfte var att utvärdera genomförbarheten av individuell kognitiv beteendeterapi (KBT) hos PmMS och depressiva symtom. **Metod:** Studie I, II och III baseras på en 10-årsuppföljning av ett populationsbaserat urval av PmMS i Stockholms Län (n=166). Totalt 123 PmMS deltog i 10-årsuppföljningen. Information om sjukdomsspecifika variabler, kontextuella faktorer, olika aspekter av funktionshinder, HRLK och patienttillfredsställelse med vård samlades in genom hembesök vid baslinjen och vid 10-årsuppföljningen genom tester och frågeformulär. Information om datum för död och dödsorsak samlades in via Socialstyrelsens register. Information om utnyttjande av vård samlades in genom registerdata från Stockholms Läns Landsting. Rekrytering av deltagare till studie IV (n=15) genomfördes vid Neurologiska kliniken, Karolinska Universitetssjukhuset. Inklusionskriterier var en säkerställd och informerad MS diagnos och depressiva symtom motsvarande milda till måttliga. Interventionen bestod av 15-20 individuella behandlingstillfällen med en legitimerad psykoterapeut. Information om genomförbarhet av metoder och mätinstrument samt förändring i depressiva symtom och andra funktionshinder samlades in. Uppföljning genomfördes tre veckor och tre månader efter avslutad intervention. **Resultat:** Det var ingen skillnad i förekomst av PmMS med kognitiv funktionsnedsättning, depressiva symtom eller med inskränkt delaktighet i sociala/livsstils aktiviteter över tid. Det var en ökad förekomst av PmMS med begränsad finmotorik och gångförmåga och med aktivitetsbegränsningar i dagligt liv. HRLK var överlag stabil över tid. Utnyttjandet av vård under tidsperioden var omfattande och inkluderade primärvård, specialistvård och inneliggande sjukhusvård. Högre sjukdomsgrad var en viktig variabel för att predicera förekomst av funktionshinder. Låg coping förmåga, depressiva symtom och kognitiv funktionsnedsättning var viktiga variabler för att predicera en minskning av HRLK. Låg coping förmåga, depressiva symtom, begränsad finmotorik och en ökning av sjukdomsgraden var viktiga variabler för att predicera utnyttjande av vård. Tillfredställelse med vården var stabil över tid. Metoderna i studie IV var överlag genomförbara. **Konklusion:** Medvetenheten om de psykologiska aspekterna av MS behöver öka bland vårdpersonalen. Det finns en möjlighet att öka HRLK genom att minska effekterna av modifierbara faktorer och genom att tillgodose behovet av omgivningsfaktorer som syftar till att minska funktionshinder. Genom full delaktighet mellan PmMS och deras vårdgivare och genom att införa strategier för att koordinera vården mellan olika vårdgivare finns en möjlighet att förbättra och effektivisera vården för PmMS. Individuell KBT är genomförbart för PmMS.

LIST OF SCIENTIFIC PAPERS

I. Chruzander C, Johansson S, Gottberg K, Einarsson U, Fredrikson S, Widén Holmqvist L, Ytterberg C. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in disability and the value of different factors in predicting disability and mortality. *J Neurol Sci. 2013 Sep 15;332(1-2):121-7.*

II. Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widén Holmqvist L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life. *J Neurol Sci. 2014 Apr 15;339(1-2):57-63*

III. Chruzander C, Johansson S, Gottberg K, Einarsson U, Hillert J, Widén Holmqvist L, Ytterberg C. A 10-year population-based study of people with multiple sclerosis in Stockholm, Sweden: Use of and satisfaction with care and the value of different factors in predicting use of care. *Submitted.*

IV. Chruzander C, Gottberg K, Ytterberg C, Backenroth G, Fredrikson S, Widén Holmqvist L, Johansson S. A single-group pilot feasibility study of cognitive behavioural therapy in people with multiple sclerosis with depressive symptoms. *Submitted.*

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
BDI	Beck Depression Inventory
BI	Barthel Index
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CNS	Central Nervous System
EDSS	Expanded Disability Status Scale
FAI	Frenchay Activities Index
HADS	Hospital Anxiety and Depression Scale
HR	Hazards Ratio
HRQL	Health Related Quality of Life
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartil range
KI	Katz ADL Index Extended
LMCA	Lindmark Motor Capacity Assessment
MMSE	Mini Mental State Examination
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale-29
NHPT	Nine Hole Peg Test
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
PwMS	People with Multiple Sclerosis
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SIP	Sickness Impact Profile
SOC	Sense of Coherence Scale
WHO	World Health Organisation

1 INTRODUCTION

The starting point for this thesis began in the late 1990 which was the time when the Stockholm MS study was conducted, a cross-sectional population-based study of people with multiple sclerosis (PwMS) living in Stockholm County. The results from the Stockholm MS study gave raise to many further research questions including detailed knowledge of the progress of various disabilities in people with PwMS, of potential changes in health related quality of life and in use of and patient satisfaction with care in a long-term perspective. It was also found that there was a need to increase knowledge of variables important to predict changes in these outcomes. In addition, one of the main findings from the Stockholm MS study was the high occurrence of PwMS with depressive symptoms. It was also found that many PwMS in the Stockholm MS study were dissatisfied with the accessibility to psychosocial support/counseling.

In this thesis I wanted to address the research questions that arose from the Stockholm MS study and also to explore the feasibility and effectiveness of different treatment methods for alleviating depressive symptoms in PwMS. Therefore, a pilot study exploring the feasibility of face-to-face cognitive behavioural therapy (CBT) is included in this thesis.

2 BACKGROUND

2.1 MULTIPLE SCLEROSIS

MS is a neuroinflammatory and neurodegenerative disease, characterised by demyelination and axonal degeneration in focal areas of the central nervous system (CNS). Clinical events are usually associated with areas of inflammation in the CNS (1, 2). Even though the cause of MS is not yet fully understood, the CNS damage is believed to result from an immune-mediated process, resulting from an interaction between genes and environmental variables such as smoking, infections and a deficit of vitamin D (3). At present, the understanding of how environmental variables may impact the immune function in PwMS on a cellular and molecular level is emerging (3).

Even though MS is not considered to be a fatal disease and premature deaths are more likely to be due to secondary complications (4), life expectancy is decreased in PwMS compared to the general population (5, 6). The clinical course of MS varies from episodes of symptoms with total resolution to permanent severe disability. The initial course is often characterised by relapses of neurological focal deficits followed by a variable degree of recovery called relapsing-remitting MS. About 85 to 90 % of the PwMS initially demonstrate a relapsing-remitting pattern (2). Eventually, about 10 to 20 years after onset the majority of the PwMS enter a progressive phase called secondary progressive MS with an insidious increase in the neurological deficits. About 10 to 15% of the PwMS have a primary progressive course characterised by a gradually progressive clinical course directly from onset (1). Diagnosis of MS is based on established clinical and laboratory criteria (7).

There is yet no cure for MS, however a growing body of evidence has shown that the use of immunomodulatory treatment reduces the early clinical and sub-clinical disease activity that is thought to contribute to long-term disability (8-10). Still, the prognosis at the individual level is highly variable and unpredictable and adherence to treatment may be challenging (11). Progressive disability will therefore remain the characteristic experience for most PwMS over decades.

MS is recognised worldwide but the incidence and prevalence varies between regions, populations and between the sexes. The female to male ratio is reported to be from 2 to 3:1. Caucasians are affected more than other racial groups (12) and the prevalence increases with increased distance from the equator with parts of northern Europe being high risk areas (13). In Europe, the annual incidence estimate of MS varies from 1.28/100 000 to 9.6/100 000 and the prevalence from 20/100 000 to 200/100 000 (14). In Sweden, the prevalence of MS is reported to be around 189/100 000 which indicates that almost 20 000 people are living with MS in Sweden and the female to male ratio is reported to be 2.35:1 (15).

MS is commonly diagnosed in people who are 20-40 years of age and is the leading cause of neurological disability in younger adults. The disease may cause a wide range of symptoms including proprioceptive impairment, depression, fatigue, bladder- bowel and sexual impairments and cognitive- and motor impairments (16) with a significant impact on health related quality of life (HRQL), working ability and ability to fulfil household responsibilities (17). MS also threatens personal autonomy and independence, dignity and life planning (18).

2.2 INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH

The International Classification of Functioning, Disability and Health (ICF) (19) is a framework which provides a scientific classification system for describing health and disability based on a biopsychosocial model of disability and health (20). The ICF comprises of two parts with two components respectively, of which the first is ‘Functioning’, a comprehensive umbrella term, including the components: body functions/body structures and activities and participation. The second part is ‘Contextual factors’, also a comprehensive umbrella term, including the components: environmental and personal factors. ‘Disability’ is also a comprehensive umbrella term used for the impairment of body function/body structures and activity limitations and participation restrictions. The environmental factors make up the physical, social and attitudinal environment in which people live and can have a hindering or a facilitating impact. Personal factors are the particular background of an individual´s life and living, for example age, sex and coping capacity. Functioning and contextual factors dynamically interact which each other in a complex relationship, as demonstrated in Figure 1.

In this thesis the ICF was used as a framework but the included variables were not classified in detail according to the ICF.

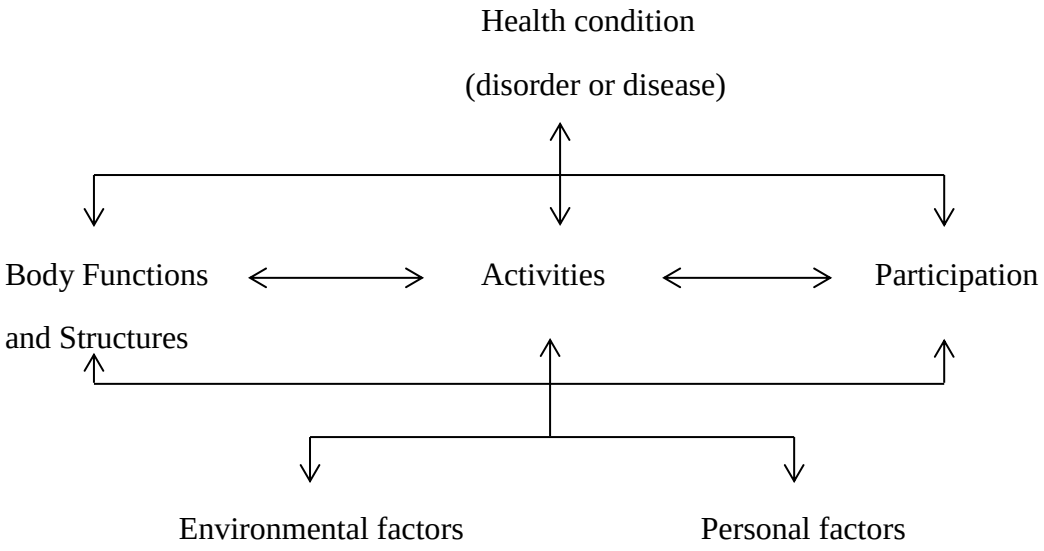

Figure 1. The theoretical model of the interactions between health condition and the components of the ICF.

2.2.1 Disability

In this thesis aspects of disability known to commonly occur in PwMS were studied including depression, impaired cognition, limitation in manual dexterity, in walking ability, in activities of daily living (ADL) and restrictions in social/lifestyle activities (21).

2.2.1.1 Depression

The diagnosis of major depression is based on the criteria in The Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-V) (22). For a major depression, a person must have experienced at least five of the nine symptoms listed in the DSM-V for a minimum of two weeks. In clinical practice screening of depression is often managed by a questionnaire instead of a diagnostic interview. Some of the defined symptoms occurring on the list of the DSM-V as well as on questionnaires might be associated with the neurological changes of MS rather than symptoms of depression, such as fatigue, impaired memory and concentration. It is important to distinguish whether the symptoms derives from MS or are signs of depression.

Depression is the most common mood disorder in PwMS (23) with an estimated prevalence ranging between 20% to 40% (24-26) and an estimated lifetime prevalence of about 50% (27). Short-term longitudinal studies (up to three years) (28-30) and one long-term longitudinal study (over 10 years) (31), have demonstrated that the occurrence of depression is fairly stable over time, however further studies with a long-term longitudinal perspective needs to confirm this finding.

The aetiology of depression in PwMS is not yet fully understood but is thought to be both a complication associated with MS and a symptom of MS (32). It has been proposed that the course of depression in PwMS differ from the course in the general population. While the general population has episodic periods of the depression, for PwMS it resembles a persistent depressive disorder category (22). The differences might partly be explained by studies using Magnetic Resonances Imaging (MRI) which have found associations between pathological MRI findings and depression in PwMS. These findings strengthen the theory of a disease specific aetiology for depression in PwMS (33, 34). However, no clear association has been found between depression and disease specific variables such as disease severity, disease course or disease duration (24, 35). A short-term longitudinal population-based study found an association between increased disease severity and depressive symptoms (28) while a long-term longitudinal study found no such association (31). Further understanding is therefore needed about the importance of different variables to predict the outcome of depression.

It has been shown that depressed PwMS do not always receive adequate treatment for depression (36) and that they are dissatisfied with the accessibility to psychosocial support from the health care system (37). If untreated, depression may lead to increased disability and worse HRQL (38). It can also lead to decreased adherence to disease modifying treatment (39) as well as an increased the risk for suicide (40).Current treatment for depression in PwMS includes antidepressant medication (41), physical exercise (42) and different psychological treatment methods (43, 44). However, further knowledge of effective treatment methods for depression in PwMS is needed.

2.2.1.2 Cognitive impairment

Cognition can be defined as all mental activities that are associated with thinking, knowing and remembering (45). Rather than a global cognitive decline, the cognitive impairment in PwMS appears to be characterised of domain-specific deficits. The most commonly impaired domains include memory and learning, information processing speed, attention, executive functions and visuospatial abilities (46, 47). Cognitive impairment has a negative impact on functioning and can disrupt several aspects of daily and social life independently of the degree of the physical disability (48). The estimated prevalence of cognitive impairment in PwMS ranges from around 40% to 70% (29, 49-52). Cognitive impairment has been reported to be present in all stages and severity of the disease (49, 53). Although previous studies have found that the proportion of PwMS with cognitive impairment increases over time (54), the amount of scientific literature with a long-term longitudinal perspective is limited and the results are inconclusive (55, 56). Further studies with long-term longitudinal perspectives are therefore needed

No clear association has been found between disease related characteristics such as disease severity or disease course and cognitive impairment (48, 57). M ale sex, however, has been found to be a predictor of cognitive impairment (58) but further insight into the importance of different variables to predict cognitive impairment is needed.

2.2.1.3 Limitation in manual dexterity

Limitation in manual dexterity can be defined as the inability to make coordinated hand and finger movements in order to grasp and manipulate objects and includes impairments in muscular, skeletal, and neurological functions (59). MS is associated with an impaired manual dexterity in grasp, lift and grip tasks in foremost dynamic tasks (60-62) and tasks such as cutting nails, peeling fruit and buttoning clothes are perceived as difficult (63). Two cross-sectional studies have reported that the prevalence of limitation in manual dexterity ranges between 73 to 76% (25, 52). There is sparse literature exploring the limitation in manual dexterity over time. One longitudinal two year study reported that almost 50% of the studied sample experienced a clinically meaningful variation in manual dexterity over time (29). To explore the long-term occurrence of limitation in manual dexterity, perspective longer than two years is needed and further studies are warranted.

2.2.1.4 Limitation in walking ability

Limitation in walking ability can be defined in terms of impaired gait patterns such as restrictions in walking speed and stride length and prolonged double support phase, all of which have been reported in PwMS (64, 65). Limitation in walking ability in terms of restrictions in walking distance is often used as a component in the assessment of disease severity (66). The prevalence of limitation in walking for PwMS is reported to be high. One cross-sectional clinical-based study of the self-perceived walking ability demonstrated that about 90% of the PwMS experienced limitation in walking (67). Another cross-sectional clinical-based study reported a prevalence of 43% (25) and one population-based study reported a prevalence of 92% (52). Differences in results can be attributed to differences in MS cohorts under study as well as different methods and instruments used. In addition, the use of a walking aid is also common among PwMS. One study reported that 73% of the PwMS used a walking aid indoors and that 77% used a walking aid outdoors (67). Walking ability is perceived as one of the most valuable activities from the perspective of the PwMS (68), and a limitation in walking may increase the risk for falls (67), increase limitation in activities of daily living (ADL) and restrict participation in social/lifestyle activities (69). Further knowledge of the progress of limitation in walking in a population-based cohort, using a long-term longitudinal perspective is needed.

Restrictions in walking distance is associated with a more severe MS (66), but to my knowledge, no studies of other variables associated with limitation in walking have been performed and further studies exploring the importance of different variables to predict limitation in walking are needed.

2.2.1.5 Limitation in activities of daily living

ADL can be grouped into personal ADL and instrumental ADL. Personal ADL represent activities that are performed daily and that are necessary for independent living, such as bathing, dressing, eating, transfer from bed to chair, continence and toileting (70). Meanwhile instrumental ADL represent activities that are more comprehensive and necessary for the

individual in order to live independently in the society, such as household activities and transportation (71). Household management, personal care and functional mobility have been reported as the ADL that are perceived by the PwMS as the most difficult to perform (72).One cross-sectional and one short-term (two years) longitudinal studies have reported that about 50% of the PwMS experience limitations in P-ADL (25, 69) and about 70% in I-ADL (73). Information on the long-term progress (10 years) of ADL in PwMS is sparse although two studies with a follow-up time of 10 years found that in clinical-based cohorts of PwMS, limitation in ADL occurs early after diagnosis and that these limitations increases over time (74, 75). It is also important to study changes in occurrence of limitation in ADL in a population-based cohort.

In different clinical contexts male sex has been found to be associated with limitations in ADL (72, 76) while no associations have been found between limitations in ADL and age, disease severity and living arrangement (72). Further studies, in other contexts, are needed to explore the importance of different variables to predict limitation in ADL.

2.2.1.6 Restrictions in social/lifestyle activities

Social/lifestyle activities are more complex activities compared to ADL and require decision-making and organisation on the part of the individual. Social/lifestyle activities can include working, gardening and going out to eat at a restaurant.

Cross-sectional studies have demonstrated that about 50 to 75% of the PwMS experience restrictions in social/lifestyle activities (25, 69). The scientific literature exploring the long-term longitudinal progress of restrictions in social/lifestyle activities in PwMS is sparse. One study with a follow-up of 10 years found that there was a low level of participation in social/lifestyle activities soon after an MS-diagnosis and there was a further decline during the course of the disease (74). However, the results were based on a clinical-based cohort of PwMS and further studies using a population-based longitudinal perspective are needed. A number of studies have found that MS has a devastating impact on working ability (77-79). These studies also found that not using immunomodulatory treatment (77), older age (77), lower level of education (78), a more severe MS (77, 78) longer disease duration (77, 78) and fatigue (78) were negatively associated with working ability. However, further studies are needed to explore the importance of different variables to predict overall restrictions in social/lifestyle activities.

2.2.1.7 Mortality

An observational population-based study has reported a decrease in life expectancy of 6 years in PwMS (5) and another study reported an almost threefold mortality rate in PwMS compared to the general population (6). MS itself is not considered a fatal disease and premature deaths are more likely to be due to secondary complications, such as respiratory or infectious diseases.

It is possible that the use of immunomodulatory treatment has a positive effect on life expectancy (80) and future studies on the long-term effects of disease modifying treatment effects is warranted. The influence of age at diagnosis, sex and disease-specific variables on mortality in PwMS has been well documented; primary progressive disease course is associated with higher mortality from disease onset compared to other disease courses, although no differences in mortality between disease courses have been reported from birth to time of death (5, 6). Inconclusive results regarding the association between sex and mortality are reported (81, 82) and changes in the female to male ratio in MS have been reported as an attributional explanation for these inconclusive results (83). However, the association between mortality and other personal variables such as coping capacity and aspects of impairment such as cognitive impairment and depressive symptoms has not yet been explored but would give valuable information of potential risk variables for mortality in PwMS and further studies exploring these associations are therefore warranted.

2.2.2 Contextual factors

Contextual factors included in this thesis were age, sex and coping capacity, work status and level of education.

2.2.2.1 Sense of coherence

The salutogenic model sense of coherence (SOC) introduced by Antonovsky describes the degree to which a person views the world as meaningful, comprehensive and manageable (84) and refers to capacities that facilitate coping with stressors. A stronger SOC implies that the person has more resources to cope with stressful situations, such as living with a chronic disease such as MS. The SOC is thought to be determined up to the age of 30 and then becomes stable over the life course, although it has been reported to change due to a traumatic experience (85). Two cross-sectional population-based studies of PwMS reported that a weak SOC was associated with depressive symptoms (86) and a lower HRQL (87). A two year longitudinal study found that a low to moderate SOC was associated with an increased perceived psychological impact of MS (88). Further studies are needed to investigate the importance of coping capacity in predicting the outcome of changes in different aspects of disability, in mortality rates, in HRQL and in the use of care.

2.3 HEALTH RELATED QUALITY OF LIFE

Health is defined by the World Health Organization as ‘a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity’ (89).

HRQL is a narrower concept than quality of life and includes aspects of quality of life that are related to a person’s health (90-92). Measuring HRQL is a method to measure to what extent disease and treatment influence important domains of functioning and health (93) and has become widely used in clinical trials, effectiveness studies and studies of quality of care since measurements of HRQL has been found to be responsive to clinically important changes (90). The term ‘self-reported functioning’ is defined as a limited part of HRQL

referring to ‘health status’ and functioning (94). Despite the use of different terms, they all incorporate the perspective of the individual. There are several methods of measuring HRQL in terms of choice of questionnaire, which may be generic (95) (96), or disease specific (97).

Cross-sectional studies in Europe and Canada have demonstrated that HRQL is negatively affected in PwMS compared to the general population (87, 98, 99). Current findings of changes in HRQL in a short-time perspective (2-5 years) suggest that although the physical dimension of HRQL deteriorates over time (100-102), the psychosocial domain remains stable or improves (88, 101, 102). However, whether these findings in HRQL are consistent in a long-term perspective (10 years) has not been thoroughly studied and further investigations are needed.

Depressive symptoms (88, 99, 102) and cognitive impairment (88, 99) have frequently been shown to predict deterioration in HRQL in studies with a short-term perspective. There are also studies which report the impact of a weaker coping capacity (88), a more severe MS (99), male sex (99) and lower education (99, 103) to predict deterioration in HRQL in a short-term perspective. However, to my knowledge it has not yet been determined whether these findings are consistent in a long-term perspective (10 years) and further studies are therefore needed.

2.4 CARE

2.4.1 Definition of care

Sweden is divided into 20 County Councils of which the Stockholm County Council is responsible for the tax financed care in Stockholm County. The use of care services that was studied in this thesis includes all the tax financed care for which the Stockholm County is responsible, i.e. primary care and hospital outpatient and inpatient care.

The Departments of Neurology (including Karolinska University Hospital and Danderyd Hospital) have the main responsibility for the specialist MS care in Stockholm County. Besides MS-specific treatment and rehabilitation provided by the MS-team at the Departments of neurology, there are a variety of other care services involved in the care for PwMS, for example within the primary sector or outpatient and inpatient rehabilitation centres.

In addition to the care for which the Stockholm County is responsible, the municipalities in Stockholm County are providers of services such as home care and personal assistance, safety alarm systems and home adaptions. However, these care services, provided by the municipalities, are not included in the definition of care in this thesis.

2.4.2 Use of care

Chronic diseases, including MS, offers significant challenges to health care systems (104). Previous cross-sectional and short-term (up to three years) studies have found that PwMS use a large amount of care (105, 106) however further studies are needed to investigate the use of

care in a long-term perspective. A more severe MS has been reported to be associated with a higher cost and a higher total amount of care used (105). Short-term longitudinal studies (two years) have found that fatigue (107) and depressive symptoms (108) are associated with a higher use of care. However, further knowledge is needed on the importance of other variables to predict the use of care.

2.4.3 Guidelines for care

There are yet no national guidelines for the treatment of MS in Sweden, however in 2014 the Swedish Government has launched a national strategy for the prevention and treatment of chronic diseases including MS. The aim of the strategy is to develop health care for people with chronic diseases and thereby create the prerequisites for a sustainable, effective and equal health care. MS is one of the prioritised diagnoses and national guidelines will be developed within the next two years (109).

According to the current clinical guidelines established by the Swedish MS-association (110), the specialist MS care should be organised in multi-disciplinary teams including neurologists, nurses, physiotherapists, occupational therapists, speech therapists and welfare officers with a special interest in MS care and should include MS-specific treatments, symptomatic treatments (including spasticity, pain, fatigue and bladder impairment) and rehabilitation. The guidelines also state the need for continuous access to these multi-disciplinary teams during the MS-trajectory. It is possible that, due to an uneven distribution of neurologists and MS specific rehabilitation between rural and urban County Councils in Sweden, the prerequisites to follow the guidelines might differ between County Councils in Sweden.

2.4.4 Patient satisfaction with care

Patient satisfaction with care is a multidimensional concept which is becoming widely used in care services as a measure for the outcome and quality of care, and in that sense, gives health care providers information which can be used as the means for improved care. It is considered a personal rating of care services and providers (111) but it can also provide information on the person, as their rating may be influenced by their expectations, preferences and standards (111). A number of studies have demonstrated that PwMS are not satisfied with several areas of care, for example; accessibility of care (37, 112) and psychosocial support (37, 113, 114); advice on social security matters; and continuity of rehabilitation services (114) and participation in planning care (37, 113). Considering that MS is a progressive disease and that different health care needs may occur during the MS trajectory, it is important to investigate the satisfaction with care in a long-time perspective, which has not been done, at least not to my knowledge.

2.5 COGNITIVE BEHAVIOURAL THERAPY FOR PEOPLE WITH MS AND DEPRESSIVE SYMPTOMS

CBT is a psychological treatment method recommended for people with mild to moderate depression by the Swedish National Board of Health and Welfare (115). The CBT model

includes behavioural activation, cognitive interventions and depressive symptoms relapse prevention (116). Behavioural activation means agreed-to tasks for the patient to perform between sessions, such as basic household tasks or participation in a social activity, aimed at breaking avoidance behaviours that perpetuate the depressive symptoms. The agreed-to tasks are followed up with the help of Socratic questions, aiming at changing negative automatic thought processes (116). Usually, a CBT intervention starts with two to three enrolment sessions, including informing patients of CBT, assessing of the individual's ability and motivation to assimilate CBT and mapping (conceptualisation and behaviour analysis) for goal setting as well as socialisation to the CBT model and psychological education.

However, the recommended guidelines from the Swedish National Board of Health and Welfare are based on studies of people without other chronic physical health problems, so CBT may therefore not be appropriate or effective in people with a chronic physical health problem (117). The United Kingdom National Institute for Health and Clinical Excellence (NICE) (118) recommends CBT for the treatment of depression in people with a chronic physical health problem, such as MS, since it offers one of the few ways in which the HRQL in this group can be improved. A Cochrane review proposed that CBT might be beneficial for PwMS with depressive symptoms, but stated that the evidence is weak due to small study populations, different outcome measurements and different types of CBT used (group-, face-to-face, internet- or telephone-based interventions) and that further studies are warranted (119).

2.6 RATIONALE FOR THE THESIS

The majority of the PwMS will live with the disease over decades and experience various changes and increases in several aspects of disability over time and therefore have various needs for different care service over time. For care services to be able to organise and provide the appropriate care to meet the needs of the PwMS, it is essential to have detailed knowledge of changes in the occurrence of different aspects of disability over the long-term (10 years). A deeper understanding of the importance of different variables for predicting these changes is also needed. In addition, the patient's perspective on their health changes, captured by measuring HRQL, and patient satisfaction with care services, provides important insights to the experience of living with MS and are therefore essential to incorporate when evaluating, developing and improving care services for PwMS. In order to create the prerequisites for a long-term sustainable effective and equal health care for PwMS, a large knowledge base on the use of care as well as predictors on use of care in a long-term perspective is needed.

Finally, the high prevalence of depressive symptoms among PwMS highlights the urgent need for care services to provide effective treatment methods for the depressive symptoms. CBT has a potential to decrease depressive symptoms but further knowledge is needed about what methods of CBT that is most effective, about the intensity of CBT and about which subgroups of PwMS would benefit from this treatment and . To gain this knowledge, a pilot feasibility study first needs to be undertaken.

3 AIMS

The overall aim in this thesis was to explore disability, HRQL, the use of care and patient satisfaction with care over a 10 year period in a population-based cohort of PwMS in Stockholm County. Also, this thesis aimed to explore the importance of different variables in predicting the outcome of disability, HRQL and use of care. In addition, the aim was to evaluate the feasibility of face-to -face CBT for alleviating depressive symptoms in PwMS.

Specific aims were:

I. In a 10 year follow-up of a population-based cohort of PwMS: to explore changes in occurrence of disability, and to explore the importance of contextual factors and disease-specific variables and depressive symptoms in predicting changes in occurance of disability and to explore the importance of personal and disease-specific variables, depressive symptoms and cognitive impairment in predicting mortality rates.

II. In a 10 year follow-up of a population-based cohort of PwMS: to explore changes in HRQL, and to explore the importance of contexutal factors, disease severity, depressive symptoms and cognitive impairment in predicting changes in HRQL.

III. In a 10 year follow-up of a population-based cohort of PwMS: to explore the use of care, and the importance of contextual factors and disease-specific variables and functioning in predicting the use of care, and to explore satisfaction with care from the perspective of the PwMS.

IV. To evaluate the feasibility of face-to-face CBT for PwMS with depressive symptoms in a single-group pilot feasibility study and the feasibility of methods and measurements used and the outcomes of face-to-face CBT on depressive symptoms, other disabilities and HRQL before conducting an effectiveness study of comparative methods of face-to-face CBT.

4 MATERIAL AND METHODS

Study I, II and III in this thesis has the same methodological approach comprising a population-based observational study design with a follow-up time of 10 years. The design of study IV comprises a single-group pilot feasibility study.

STUDY DESIGN

4.1.1 Observational longitudinal study design

With an observational longitudinal study design, the researcher collects information about the participants and their exposures at baseline, let time pass and then assess the occurrence of outcomes. In observational studies, data can be used to explore new ideas about potential associations between exposure at baseline and outcomes at follow-up (120, 121). In study I, II and III in this thesis, an observational study design was used with a follow-up time of 10 years. At baseline, data on potential exposures were collected and at the 10-year follow-up, data on the outcomes was collected. In addition, the design also allows studying the change in outcome or the change in occurrence of outcome.

4.1.2 Feasibility study design

Due to the complexity of evaluating the effectiveness of a psychological intervention, a pilot study in which the feasibility of a CBT intervention is studied must be undertaken, in order to plan for a study in which the effectiveness of treatment can be studied. A pilot feasibility study may answer questions about the feasibility of methods and instruments used and hopefully provide answers on how to deal with potential problems (122).

4.2 PARTICIPANTS AND PROCEDURES

4.2.1 Study I, II and III

Study I, II and III is based on a 10-year follow-up of a population-based study of PwMS in Stockholm County, Sweden, for which the recruitment process has been described in detail previously (52). In brief, the PwMS included at baseline (from September 1999 to September 2002) were recruited from a temporary data pool consisting of 2129 patients from all hospital neurology clinics in Stockholm County, in order to obtain the highest possible population-based ascertainment, a random sample was drawn, representing 15% (n=321) of the data pool. Inclusion criteria were: a definite and informed diagnosis of MS, being a resident in Stockholm County and having no diagnosis of other severe neurological or psychiatric illness according to the physician. Of the 196 PwMS who fulfilled the inclusion criteria, 166 (85%) gave informed consent and agreed to participate. In order to collect data for the 10-year follow-up, the same PwMS were identified and those still alive were contacted by post. Data collection was performed by home visits at a date 10 years ± 6 months after baseline (from

May 2009 to February 2012). Data were obtained using structured face-to-face interviews including the same tests and questionnaires, in a standardised order, as was used at baseline. In addition, for study I, register-based data including cause and time for death was collected from the National Board of Health and Welfare and for study III, register-based data including use of care was collected from the Stockholm County Council.

4.2.2 Study IV

4.2.2.1 Recruitment of patients

Recruitment of patients to study IV was conducted at the Department of Neurology, Karolinska University Hospital Huddinge. The recruitment process intended to imitate clinical praxis for identifying PwMS with depressive symptoms i.e. those PwMS who either by telephone or by hospital outpatient visit were in contact with a nurse or a neurologist specialized in MS and perceived to be in need of psychological counselling due to depressive symptoms were asked to participate. The pilot study aimed at including a strategic sample of 15 PwMS in order to capture a variation regarding age, sex and disease severity. After giving informed consent those PwMS who agreed to participate were contacted by the study coordinator to schedule a date for screening and, if included in the study, for baseline face-to-face data collection. All assessments were performed at the Department of Neurology, Karolinska University Hospital, Huddinge.

4.2.2.2 Inclusion/exclusion criteria

Inclusion criteria were a definite and informed MS-diagnosis and sub-threshold to moderate depressive symptoms comparable to a clinically important level on a validated depression scale. Exclusion criteria were having age below 18 years, other severe neurological or psychiatric disease according to their physician, antidepressant medical treatment prescribed less than three months before inclusion and/or other ongoing psychological treatment. PwMS that exhibited depressive symptoms greater than moderate, were re-remitted to their neurologist.

4.2.2.3 Recruitment of therapists

Three psychologists licensed as psychotherapists and specialized in performing CBT were recruited to perform the CBT intervention (they are from now on referred to as therapists). The recruitment of therapists was conducted using an advertisement at the website of the Swedish Association for Behaviour Therapy. A total of four therapists were interested in participating and were interviewed regarding previous experiences in treating PwMS with depressive symptoms and the physical accessibility at their clinical practices. One therapist withdrew her application and a total of three therapists were recruited.

4.2.2.4 Intervention

The CBT intervention was scheduled to comprise 15 to 20 individual face-to-face sessions (50 minutes each) with approximately one session/week. The intervention was initiated with

three enrolment sessions, including patient information of CBT, motivation to and assessment of the individual's ability to assimilate the CBT intervention. Furthermore, a mapping (conceptualization and behavior analysis) for goal setting as well as socialization to the CBT model and psychological education were conducted during the enrolment. The CBT included behavioural activation, cognitive interventions and depressive symptoms relapse prevention (116). Behavioural activation means agreed-to tasks for the PwMS to perform between sessions, such as basic household tasks or participation in a social activity, aimed at breaking avoidance behaviors that perpetuate the depressive symptoms. The therapists followed up the tasks with the help of Socratic questions, aiming at changing negative automatic thought processes (116).

4.2.2.5 Follow-up

Follow-ups were conducted face-to-face three weeks and three months after completed intervention, including the same tests and questionnaires as were used in the baseline data collection.

4.3 TESTS AND QUESTIONNAIRES

For study I to III, the same tests and questionnaires as in the baseline data collection was used. These standardised tests and questionnaires were employed to collect data reflecting aspects of disability commonly affected in PwMS. Disease-related variables and contextual factors were also collected as were data on HRQL and patient satisfaction with care. As in study I, II and III, study IV included instruments reflecting aspects of disability commonly affected in PwMS with the addition of variables reflecting feasibility of methods and tests and questionnaires used. Table 1 presents the tests and questionnaires used in study I, II, II and IV.

The selection of the tests and questionnaires used was based on recognised reliability and validity.

4.3.1 Disease-specific characteristics

Disease course and the use of immunomodulatory treatment were determined by the senior neurologist using medical notes. Information about concurrent diseases was collected at the home-visits.

4.3.1.1 Disease severity

4.3.1.1.1 The Expanded Disability Status Scale

Disease severity was assessed by the data-collectors at the home visits using the Expanded Disability Status Scale (EDSS) (66) and was then verified by the senior neurologist. The EDSS was developed in order to assess disability in PwMS. The scale ranges from 0 to 10 were 10 represents death due to MS. The EDSS includes assessment of pyramidal, cerebrellar, brain steem, bowel and bladder, visual and mental functions, assessment of

walking distance and ambulation. The validity and reliability of the EDSS has been questioned (123, 124).

In study I and IV the EDSS was referred to as "disease severity" and in study II and III as "MS disability". From here on, the abbreviation "EDSS" will be used when referring to disease severity.

Table 1. Tests and questionnaires used in study I, II, III and IV.

Tests and questionnaires	Study I	Study II	Study III	Study IV
Questions concerning contextual information	X	X	X	X
Sense of Coherence Scale	X	X	X	X
Beck Depression Inventory-II	X	X	X	X
Hospital Anxiety Depression Scale				X
Fatigue Severity Scale				X
Symbol Digit Modalities Test	X	X	X	X
Mini Mental State Examination	X			
Lindmark Motor Capacity Assessment				X
Nine-Hole Peg Test	X		X	X
2X5 m walk test	X		X	
10 m walk test				X
The Katz Extended ADL Index	X		X	X
The Barthel Index	X			X
Frenchay Activities Index	X		X	X
Questionnaire on patient satisfaction with care			X	
The Sickness Impact Profile		X		
The EuroQol-5D		X		X
The Multiple Sclerosis Impact Scale				X

4.3.2 Disability

4.3.2.1 Depressive symptoms

In clinical practice, screening of depression is often managed by a questionnaire instead of a diagnostic interview. The term "depressive symptoms" have been used in this thesis to describe what the questionnaire measure since no diagnostic interviews have been employed.

4.3.2.1.1 The Beck Depression Inventory-II

The Beck Depression Inventory II (BDI-II) was used to assess depressive symptoms (125). The BDI-II consists of 21 self-rated statements related to depression. The ratings range from 0 (absent) to 3 (severe), or for one item from 0 (absent) to 2 (severe). The individual is instructed to rate each statement and a total score, ranging from 0 to 62 is calculated. The inventory is recommended and widely used to asses depressive symptoms in PwMS (36, 126) and the validity (70, 127) and reliability (70) are considered good.

4.3.2.1.2 The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (128) was used to assess anxiety and depressive symptoms. The HADS consist of two sub-scales, one related to anxiety and the other to depressive symptoms, with a total of 14 self-rated statements. The ratings range from 0 (absence of a symptom or the presence of positive features) to 3 (maximal presentation of a symptom or the absence of positive features). The individual is instructed to rate each statement and a total score on each subscale, ranging from 0 to 21 is calculated. Validity (129) and reliability (130) is reported to be good.

4.3.2.2 Fatigue

4.3.2.2.1 The Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a test for assessing perceived level of energy-fatigue. The FSS reflects the impact of fatigue on daily functions (131). The FSS includes nine statements which are rated on a scale from 1 (strong disagreement) to 7 (strong agreement). The FSS score is the mean of all statements. The FSS is found to be valid and reliable (131, 132).

4.3.2.3 Cognitive impairment

Aspects of cognitive impairment were assessed by the Symbol Digit Modalities Test (SDMT) (133) and the Mini Mental State Examination (MMSE)(134) .

4.3.2.3.1 The Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) (133) is a recommended test for assessing attention and processing speed in PwMS (51). The test consists of digits paired with geometric symbols. The respondent is asked to replace as many as possible geometric symbols on a given time. The SDMT was primarily administrated in a written response but for those PwMS unable to write, the SDMT was administrated in a verbal response. The SDMT is considered as a reliable test (135) and the validity is reported to be equal to that of other screening tools for cognitive impairment in PwMS (136). The SDMT is a recommended screening tool for cognitive impairment in PwMS (137).

4.3.2.3.2 The Mini Mental State Examination

The Mini Mental State Examination (MMSE) is a widely used test in clinical settings for screening of general cognitive performance (134). Reliability and validity of the MMSE is considered good (70).

4.3.2.4 Impaired global motor capacity

4.3.2.4.1 The Lindmark Motor Capacity Assessment

The Lindmark Motor Capacity Assessment (LMCA) (138) was used comprising the sub-scales for active movements and co-ordination in upper and lower extremities and for balance and mobility. The items are mostly scored on a four-point scale from 0 (no function to 4 (normal function). A summation of the sub-scales, ranging from 0 to 258, is then calculated. The LMCA is considered valid and reliable (139, 140).

4.3.2.5 Limitation in manual dexterity

4.3.2.5.1 The Nine-Hole Peg Test

The Nine-Hole Peg Test (NHPT) was used to assess limitation in manual dexterity (141). The NHPT consists of a board with nine holes and nine pegs and the instructions for the NHPT is to, with one hand at a time, pick up the pegs one-by-one and insert them into the holes on the board. The individual is asked to perform the task as fast as possible and the sequence is timed with a stopwatch. The NHPT is widely used and is recommended for use in PwMS (137) and is considered valid and reliable (141).

4.3.2.6 Limitation in walking

4.3.2.6.1 The 10-Meter Walk Test

For study I and III, the 10-meter walk test was performed with a turn on a five-meter course (142). The reason for this was the test was performed in a home environment where a 10-metre distance may not be available. The individual starts and stops in a standing position and is instructed to walk as fast as possible, without risking to fall. Walking aids are allowed and noted. A stopwatch was used and the time needed to complete the walk is recorded in seconds. The test is considered valid (142) and reliable (143).

4.3.2.7 Limitations in activities of daily living

4.3.2.7.1 The Katz Extended ADL Index

The Katz Extended ADL Index (KI) was used to assess personal and instrumental ADL (144). The KI consist of six personal activities including feeding, bathing, dressing, continence, toileting and transfer; and of four instrumental activities including: cooking, cleaning, transportation and shopping. The items are scored 1 (is dependent) or 2 (is independent). The reliability and validity is reported to be sufficient (145).

4.3.2.7.2 The Barthel Index

The Barthel Index (BI) was used to asses personal ADL (146). The BI consists of 10 items including: feeding, bathing, grooming, dressing, bowel- and bladder functioning, toilet use, transfer, mobility and stairs. The items are scored 0 (is dependent), 5 (need assistance or supervision from another person), or 10 (is independent). The BI is considered reliable (147) and the validity is reported to be equal to that of other tools of assessing personal ADL (148).

4.3.2.8 Restrictions in social/lifestyle activities

4.3.2.8.1 The Frenchay Activities Index

The Frenchay Activities Index (FAI) was used to assess frequency of social/lifestyle activities (149). The FAI consists of 15 items relating to activities that requires initiative and organisation on the part of the individual. The scoring is based on the frequency with which an item has been performed during the last three or six months from 0 (inactive) to 3 (highly active). A total score is then calculated. The FAI was originally developed for use in the stroke population but have also been used in studies including other conditions for example MS (25, 29, 69). The validity and reliability is reported to be good (149, 150).

4.3.3 Contextual factors

Data on age were collected from medical records. Information on level of education and work status was collected by interview at the home visits.

4.3.3.1 Coping capacity

4.3.3.1.1 Sense of Coherence Scale

The 13-item Sense of Coherence Scale (SOC) was used to assess coping capacity (84). The items are constructed as statements which the individual rates on a Likert scale ranging from 1 to 7 with anchoring responses for example “never” and “very often”. The SOC-scale is considered valid and reliable (84, 151) and is widely used in studies of people with chronic diseases including MS (86, 88, 152).

4.3.4 Health related quality of life

4.3.4.1 The Sickness Impact Profile

The Swedish version (153) of the generic Sickness Impact Profile (SIP) (96) comprises 136 pre-defined items of self-reported functioning, where the respondents answer either “yes” or “no” to each item. These items are grouped into 12 categories, belonging to either a physical dimension (the SIP Physical dimension) including Body care and movement, Mobility and Ambulation, or a psychosocial dimension (the SIP Psychosocial dimension) including Emotional behaviour, Social interaction, Alertness behaviour and Communication. The remaining five categories Sleep and rest, Home management, Work, Recreation and pastimes and Eating are termed independent categories. Scores are calculated using item weighting to indicate the relative severity implied by each statement. A total score (the SIP Total) ranging

from 0 to 100, where 0 indicates the best possible HRQL and 100 the worst, is then calculated. Reliability and validity are considered good (154). The SIP has previously been used to assess HRQL in PwMS (87, 155).

4.3.4.2 The EuroQol-5D

The generic three level version of the EuroQol 5D consists of the EQ-5D Index and the EQ Visual Analog Scale (EQ VAS) (95). The EQ 5D Index comprises five pre-defined dimensions: Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression. The respondent rates each dimension on a three level scale as having no problem, a moderate problem or a severe problem. The answers are then converted to an index value (the EQ Index) ranging from 0 (death) to 1 (full health). The EQ VAS records the respondent's self-rated health on a 20-centimeter vertical visual analogue scale with end-points ranging from 0 to 100. The single global question in the EQ VAS asks the individual to label his/her health as 'the worst health you can imagine' (0) to 'the best health you can imagine' (100). The reliability and validity has been reported to be acceptable (156).

4.3.4.3 The Multiple Sclerosis Impact Scale

The disease-specific Multiple Sclerosis Impact Scale (MSIS-29) (97) comprises of two ordinal sub-scales of which one assesses the physical impact of MS and the other the psychological impact with a total of 29 items constructed as questions. The physical subscale consists of 20 items, and the psychological subscale of nine. The response options are graded on a five-point scale ranging from 1 (not at all) to 5 (extremely). The MSIS-29 has proven to be valid and reliable for PwMS (157, 158).

4.3.5 Use of care

Data on the use of primary care, hospital outpatient care and hospital inpatient care were obtained from the computerised register at Stockholm County Council. The register contains information regarding all use of care (clinical visits and home visits, telephone consultations and inpatient days) with care providers within Stockholm County Council, and detailed information including what profession and at which clinic or department the visit concerned. Data was obtained on an individual level on all use of care during the study period (10 years).

4.3.6 Patient satisfaction with care

A questionnaire on perceived needs and satisfaction with care was used to assess satisfaction with care. The questionnaire has previously been used in studies of people with neurological disorders (159, 160) including MS (37, 113) and is based on the taxonomy of Ware (161). The taxonomy of Ware includes the dimensions: art of care (engagement/sympathy, kind treatment), accessibility, technical quality of care, finances, availability, continuity and efficacy/outcome of care. In addition, items relating to patients participation in planning care were included. The questionnaire consists of 22 statements which the individual is asked to agree or disagree with on a 5-graded scale.

4.3.7 Feasibility outcomes

The pre-specified primary feasibility outcomes of face-to-face CBT for PwMS with sub-threshold to moderate depressive symptoms included: recruitment procedure, recruitment rate, completion rate, potential adverse events and the ability to recruit therapists with the formal competence required according to the Swedish National Board of Health and Welfare (115). Feasibility of outcome methods including number of completed sessions, number and cause of late cancellations (defined as cancellation less than 24 hours before session), intensity of treatment, reason for discontinued intervention and modification of treatment was collected from a study-protocol used by the therapists who performed the CBT.

4.4 CATEGORISATION OF VARIABLES

Recommended cut-offs were used for categorisation of weak/moderate versus strong SOC and disability in mood, cognition, manual dexterity, walking speed and social/lifestyle activities which are presented in Table 2. Limitation in walking ability was either categorised using recommended age- and sex-related norms for walking speed or by the use of walking aid. Age was categorised according to the mean of the sample, and sex into female/male. When analysing work status, PwMS ≥65 years of age were excluded since this is the customary age for retirement in Sweden. Level of education was dichotomized into primary or lower secondary school and high school/university. Disease severity was categorised using the EDSS score, into Mild (0 to 3.5), Moderate (4.0 to 5.5), Severe (6.0 to 9.5). Time since diagnosis was dichotomized into shorter or longer than 10 years. Type of MS was dichotomized into relapsing/remitting and progressive which included secondary progressive MS and primary progressive MS. The use of immunomodulatory treatment and the use of antidepressant drugs, were categorised as yes or no. Progress in EDSS from baseline to the 10-year follow-up was dichotomized into no change: ≤1 points change in EDSS from baseline to the 10-year follow-up and change: >1 points change. In the absence of a recommended cut-off for the KI and the BI, the criterion dependent in one or more items was categorised as having a limitation in ADL. Satisfaction with care was dichotomized into satisfied (1 to 2 on the scale) or not satisfied (3 to 5 on the scale). Inability to walk 10 metres was set to 0 metres/second, inability to perform the NHPT was set to 0 pegs/second and inability to perform the SDMT was set to 0.

Table 2. Cut-off levels used for below normal performance of coping capacity, for depressive symptoms, cognitive impairment, limitation in manual dexterity and in walking ability, and restrictions in frequency of social/lifestyle activities.

Variable	Test or questionnaire	Cut-off level
Coping capacity	Sense of Coherence Scale	Norm data from a reference group (162). SOC weak: 13-54 points / SOC moderate or strong: 55-91 points
Mood	Beck Depression Inventory-II	Depressive symptoms: ≥ 13 / No depressive symptoms: <13[1] (36) or Severe depressive symptoms: ≥ 20 / Sub-threshold to moderate depressive sympoms: 11-19 / No depressive symptoms: < 10[2] (70)
Cognition	Symbol Digit Modalities Test	Age-related norms (133). Impairment: ≥ -1.5 SD from the mean / No impairment: <-1.5 SD from the mean
	Mini Mental State Examination	Impairment: < 28 / No impairment: ≥ 28 (162)
Manual dexterity	Nine-Hole Peg Test	Norm data from a reference group (163). Impairment: ≤ 0.5 peg /s / No impairment: > 0.5 peg/s
Walking speed	2X5 m walk test	Age- and sex-related norms (164). Limitation: ≥ -1 SD from average speed/ No limitation: < -1 SD from average speed
Frequency of social/lifestyle activities	Frenchay Activities Index	Age- and sex-related norms (150). Restrictions in frequency: < 25th percentile / Not restrictions in frequency: ≥ 25th percentile

[1]The cut-off was used in study I, II and III

[2]The cut-off was used in study IV

4.5 STATISTICAL ANALYSIS

Descriptive statistics were used in Paper I to IV. A probability value of 0.05 was considered statistically significant if nothing else is stated. Statistical analyses were performed in SPSS version 20.0 or the SAS® System 9.1.

In Study I, the sign test was used for analyses of changes in scores from baseline to the 10-year follow-up. Statistically significant changes in occurrence of PwMS with disability at baseline and at follow-up were analysed with the McNemar test. Generalised Estimating Equations (GEE) were conducted to investigate the importance of the independent variables (age, sex, coping capacity, level of education, EDSS, disease course, time since diagnosis and mood) on an increase in occurrence of PwMS with depressive symptoms (BDI-II), cognitive impairment (SDMT), limitation in walking (use of walking aid), limitation in ADL (KI), and restrictions in frequency of social/lifestyle activities (FAI) from baseline to the 10-year follow-up. Since MS is a progressive disease, time was hypothesised to have a potential to interact with the independent variables. Interactions between time and the independent variable were therefore controlled for. Independent variables at baseline were included in all the models, together with the time variable (0 and 10 year). When the interactions were significant the main effects were also retained in the final model irrespective of statistical significance. Multicollinearity between the independent variables was controlled for. The results are presented as odds ratios (OR) with 95% CI and p values. In case of significant interactions, simple effects were presented, i.e. effect of one variable holding the other variable fixed.

In order to analyse the importance of the independent variables (age, sex, time since diagnosis, EDSS, disease course, coping capacity, level of education, cognition and mood) on mortality rate, univariable Cox regression analyses were performed followed by a multivariable Cox regression. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI) and p values.

In Study II the paired t-test was used to analyse changes from baseline to the 10-year follow-up in scores regarding the SIP Total, the SIP Dimensions (Physical and Psychosocial), the EQ-5D Index and the EQ VAS. For analyses of changes in scores regarding the SIP Categories the Sign test was used. In order to quantify the change over 10 years in the SIP Total, the SIP Dimensions, the EQ-5D Index and the EQ VAS, effect sizes were calculated and interpreted using Cohen's thresholds (165).

To analyse the importance of the independent variables (age, sex, coping capacity, level of education, EDSS, depressive symptoms and cognitive impairment) to predict a change in HRQL, as measured with the SIP Total and the EQ VAS, mixed model ANOVAs with restricted maximum likelihood estimations (REML) were conducted. Time was hypothesised to have a potential to interact with the independent variables. Interactions between time and the independent variable were therefore controlled for. Independent variables at baseline were included in all the models, together with the time variable (0 and 10 year). Since it was theorised that there could be a potential interaction between coping capacity and mood, this interaction was also controlled for. Multicollinearity between the independent variables was controlled for. To make sure that the EDSS was the most appropriate disease-specific variable to be included in the REML containing all independent variables, univariate analyses with the Mann Whitney U Test and two REML with only disease-specific variables at

baseline (duration of MS, type of MS, use of immunomodulatory treatment and EDSS) as the independent variables were first conducted. The final results are presented as estimates of effects, described as changes in points from baseline to the 10-year follow-up, with 95% confidence intervals (CI) and p values for each final model. Two separate multiple linear regression analyses were conducted to ascertain the adjusted coefficient of determination (adjusted R2) of the final mixed model ANOVAs with REML regarding the dependent variables the SIP Total and the EQ VAS respectively.

For analyses of differences between survivors and deceased PwMS according to age, EDSS, outcome of the SIP Total, the SIP Physical dimension, the SIP Psychosocial dimension and the EQ VAS at baseline, the Mann Whitney U Test was used. For differences according to gender the Fischers exact test (1-sided) was used.

In Study III, descriptive statistics were used to analyse use of care (primary care; hospital outpatient care and hospital inpatient care) distributed by profession or department from baseline to the 10-year follow-up. In order to analyses the importance of the independent variables at baseline (age, sex, coping capacity, level of education, EDSS, use of immunomodulatory treatment, type of MS, time since diagnosis, mood, cognitive function, manual dexterity, walking ability, ADL, frequency in social/lifestyle activities), and progress in EDSS) on the use of care univariable and multivariable linear regression analyses were performed. Data on the use of primary care and hospital outpatient care were summarized into the dependent variable "total outpatient care" and data on all inpatient care formed the dependent variable "inpatient care". Because of highly skewed distribution of the outcome of care, the outcome data was log transformed. For each dependent variable a stepwise analysis including all independent variables was performed. The final results of the multivariable linear regression analyses are presented as regression coefficient (B) with a 95% confidence interval (CI), standardised regression coefficient (Beta) and p value.

Changes in satisfaction with care in those PwMS who reported a need at both baseline and at the 10 year follow-up were analysed using the McNemar test. To explore the use of care for PwMS satisfied versus PwMS not satisfied with the efficacy/outcome of primary care, hospital outpatient care, inpatient care and inpatient rehabilitation, the Mann Whitney U test was used.

In Study IV, the primary analysis was an intention-to-treat analysis (ITT). For missing data at follow-up, the last value was carried forward. The secondary analysis was a completers analysis including only participants who completed the CBT. Mean differences in outcomes from inclusion to follow-up were calculated. Numbers of PwMS scoring the minimum and the maximum possible scores were examined to assess the floor and ceiling effects of the measurements. Sample size calculations were conducted for two group t-test. In these calculations differences of either five, four, three or two points of the BDI-II from baseline to follow-up were tested.

4.6 ETHICAL APPROVAL

Ethical approval from the ethical committee of the Karolinska Institutet in Stockholm was obtained for all studies, dnr: 2009/3:3 (Study I, II and III) and dnr: 2011/378-31/2 (Study IV).

5 RESULTS

5.1 SAMPLE CHARACTERISTICS STUDY I, II AND III

Sample characteristics for Study I, II and III are presented together. Of the 166 PwMS included at baseline, 32 PwMS were deceased at the 10-year follow-up and 11 declined to participate. Consequently, a total of 123 PwMS was included in the 10-year follow-up. Data were collected 10 years ± 6 months after baseline data was collected. For Study I and II, four PwMS were not able to be interviewed due to severe disability and one had not answered most of the questions and was therefore excluded. For study III, one PwMS declined register-based data to be collected, and one PwMS had moved from Stockholm County and these PwMS were therefore excluded. At baseline, mean age was 49 years (SD 11), 86 (70%) of the PwMS were female and mean time since diagnosis was 18 years (SD 11). Sample characteristics are presented in Table 3.

Table 3. Number and proportion of people with MS who completed the test at both time points and sample characteristics at baseline and at the 10-year follow-up and p value for changes in sample characteristic between baseline and the 10-year follow-up, n=123.

Variable	n (%)	Baseline n (%)	10-year follow-up, n (%)	p value
Coping capacity				
SOC Low/Moderate	110 (89)	14 (13)	15 (14)	0.842
SOC High		96 (87)	95 (86)	
Level of education				
Primary or lower secondary school	118 (96)	28 (23)	27 (23)	0.802
High school/University		90 (77)	91 (77)	
Working full- or part time [1]	123 (100)	62 (56)	37 (43)	0.055
Expanded Disability Status Scale	123 (100)			
Mild		43 (35)	19 (15)	<0.001
Moderate		25 (20)	23 (19)	0.750
Severe		55 (45)	81 (66)	<0.001
Type of MS				
Relapsing/remitting	123 (100)	58 (47)	25 (19)	<0.001
Progressive		65 (53)	98 (81)	<0.001
Immunomodulatory treatment	123 (100)	49 (40)	30 (24)	<0.001

[1]Based on PwMS < 65 years, n= 109 at inclusion and n= 86 at follow-up

Those PwMS who were deceased at the 10-year follow-up were significant older and had a more severe MS disability at baseline compared to those PwMS who survived. There was no difference regarding sex.

5.2 STUDY I

5.2.1 Changes in scores

There were statistically significant changes (p value <0.001) in median scores in all areas of functioning, implying worse functioning, except in mood (p value=0.300).

5.2.2 Changes in occurrence of disability

The occurrence of PwMS with disability at baseline and at the 10-year follow-up is presented in Table 4. There was an increase in the occurrence of PwMS with disability from baseline to follow-up in all areas except in depressive symptoms, cognitive impairment assessed by the SDMT, and restrictions in frequency of social/lifestyle activities. At baseline 17 (15%) could not walk at all and at follow-up 24 (21%). Seventeen (15%) of the PwMS walked with an aid at baseline and 37 (33%) at the follow- up.

Table 4. Number and occurrence of people with MS categorised as having a disability at baseline and at the 10-year follow-up and p values for changes in occurrence with disability, n=118.

Test or questionnaire	Baseline Disability n (%)	Follow-up Disability n (%)	p value
Timed 2x5 m Walk Test	100 (85)	108 (91)	0.027
Nine Hole Peg Test	65 (55)	77 (65)	0.014
Mini-Mental State Examination	41 (35)	68 (58)	<0.001
Symbol Digit Modalities Test	49 (42)	48 (41)	1.000
Beck Depression Inventory II[1]	21[2] (18)	23[3] (19)	0.823
Barthel Index	44 (37)	73 (62)	<0.001
Katz Extended ADL Index	71 (60)	87 (74)	0.002
Frenchay Activities Index	66 (56)	73 (62)	0.345

[1]113 PwMS completed the test at both baseline and the 10-year follow-up

[2]6 PwMS used antidepressant drugs.

[3]5 PwMS used antidepressant drugs.

5.2.3 Predictors of changes in occurrence of disability

The final GEE models are presented in Table 5. EDSS at baseline was important to predict an increase in occurrence of disability in all assessed areas except depressive symptoms. The time variable interacted with ‘time since diagnosis’ for change in occurrence of PwMS with limitation in walking, and with the variable ‘age’ for change in occurrence of PwMS who were dependent in ADL. Time also interacted with the variables ‘age’ and ‘EDSS’ for

changes in occurrence of PwMS with restrictions in social/lifestyle activities. Time did not interact with any independent variable for changes in occurrence of PwMS with cognitive impairment or depressive symptoms.

Table 5. Estimated odds ratios (OR), 95% confidence intervals (CI) and p values for the predictive value of the time factor (0 and 10 year) and the independent variables on an increase over 10 years in occurrence with depressive symptoms, impaired cognition, limitation in walking, limitation in activities of daily living and restrictions in frequency of social/lifestyle activities in people with MS according to the final[1] Generalized Estimating Equation models, n=118.

Dependent variable	Independent variable categorisation	OR (CI)	p value
Depressive symptoms[2]	SOC weak	4.05 (1.38-11.85)	0.011
	SOC moderate or strong	1 (ref)	
Impaired cognition[3]	Male	2.5 (1.1-5.4)	0.023
	Female	1 (ref)	
	Moderate EDSS	2.9 (1.1-7.9)	0.036
	Mild EDSS	1 (ref)	
	Severe EDSS	3.1 (1.3-7.0)	0.008
	Mild EDSS	1 (ref)	
Limitation in walking[4]	Time since diagnosis > 10 years	1.9 (0.8-4.9)	ns
	Time since diagnosis ≤ 10 years	1 (ref)	
	Time 10-year follow up	11.3 (5.0-25.3)	<0.001
	Baseline	1 (ref)	
	≤ 10 years since diagnosis / Time:		
	10-year follow-up	30.5 (6.6-140.3)	< 0.001
	Baseline	1 (ref)	
	> 10 years since diagnosis / Time:		
	10-year follow-up	4.2 (2.4-7.2)	< 0.001
	Baseline	1 (ref)	
	Moderate EDSS	6.9 (2.1-22.8)	0.002
	Mild EDSS	1 (ref)	
	Severe EDSS	194.7 (60.1-631.1)	< 0.001
	Mild EDSS	1 (ref)	
Limitation in activities of daily living[5]	Age ≥ 51 years	1.4 (0.6-3.2)	ns
	Age < 51 years	1 (ref)	
	Time 10-year follow up	3.1 (1.7-5.9)	< 0.001
	Baseline	1 (ref)	
	Age < 51 years / Time:		
	10-year follow up	1.8 (0.9-3.6)	ns

	Baseline	1 (ref)	
	Age ≥ 51 years / Time:		
	10-year follow-up	5.5 (2.1-14.7)	< 0.001
	Baseline	1 (ref)	
	Moderate EDSS	5.2 (2.1-13.2)	< 0.001
	Mild EDSS	1 (ref)	
	Severe EDSS	45.9 (13.6-154.3)	< 0.001
	Mild EDSS	1 (ref)	
Restrictions in frequency of social /lifestyle activities[6]	Age ≥ 51 years	0.9 (0.4-2.2)	ns
	Age < 51 years	1 (ref)	
	Time 10-year follow up	1.3 (0.7-2.2)	ns
	Baseline	1 (ref)	
	Age < 51 years / Time:		
	10-year follow-up	0.6 (0.3-1.3)	ns
	Baseline	1 (ref)	
	Age ≥51 years / Time:		
	10-year follow-up	2.7 (1.1-6.9)	0.033
	Baseline	1 (ref)	
	SOC weak	3.4 (1.3-9.2)	0.015
	SOC moderate or strong	1 (ref)	
	Moderate EDSS	3.1 (1.2-8.0)	0.021
	Mild EDSS	1 (ref)	
	Severe EDSS	28.0 (9.4-83.7)	<0.001
	Mild EDSS	1 (ref)	
	Mild EDSS / Time:		
	10-year follow-up	4.3 (1.5-12.4)	0.006
	Baseline	1 (ref)	
	Moderate EDSS / Time:		
	10-year follow-up	1.5 (0.5-4.5)	ns
	Baseline	1 (ref)	
	Severe EDSS / Time:		
	10-year follow-up	0.3 (0.1-0.7)	0.004
	Baseline	1 (ref)	

[a]Independent variables and interactions with p values ≤ 0.05 were retained in the final models. When the interactions were significant the main effects also were retained in the final model irrespective of statistical significance.

[b]Timed 2X5 m Walk Test

[c]Symbol Digit Modalities Test

[d]Beck Depression Inventory

[e]Katz Extended ADL Index

[f]Frenchay Activities Index

5.2.4 Predictors of mortality

The univariable Cox regression analyses and the multivariable Cox regression model are presented in Table 6. In the multivariable model, older age and depressive symptoms at baseline were important variables to predict the outcome of mortality.

Table 6. Hazard ratios, 95% confidence intervals (CI) and p values for the association between the independent variables on mortality in people with MS over the 10-year period according to univariable analyses and the final model of the multivariable Cox regression analyses, n=155[1].

Independent variable	Variable categorisation	Univariable analyses		Final model	
		Hazard ratio (CI)	p value	Hazards ratio (CI)	p value
Age	≥ 51 years of age	3.4 (1.5-7.6)	0.003	4.6 (1.5-14.4)	0.009
	< 51 years of age	1		1	
Sex	Male	1.5 (0.7-3.6)	0.312		ns
	Female	1			
Sense of coherence	Weak	1.3 (0.4-4.5)	0.650		ns
	Moderate or strong	1			
Education	Primary/lower secondary school	1.4 (0.7-3.0)	0.349		ns
	High school or university	1			
Time since diagnosis	> 10 years	1.9 (0.9-4.1)	0.078		ns
	≤ 10 years	1			
Disease severity	EDSS severe	4.0 (1.4-11.6)	0.009		ns
	EDSS moderate	0.9 (0.2-4.9)	0.898		
	EDSS mild	1			
Disease course	Progressive	3.9 (1.5-10.1)	0.005	3.3 (0.9-11.5)	0.066
	Relapsing-remitting	1		1	
Cognition	Cognitive impairment	1.4 (0.6-3.0)	0.431		ns
	No cognitive impairment	1			
Mood	Depressive symptoms	1.8 (0.7-4.8)	0.204	2.7 (1.04-7.24)	0.041
	No depressive symptoms	1		1	

[1]The multivariate Cox regression analyses included all PwMS available at baseline except the 11 PwMS who declined to participate in the 10-year follow-up.

5.3 STUDY II

5.3.1 Changes in health related quality of life

5.3.1.1 The Sickness Impact Profile

Total score, dimensions and categories of the SIP are presented with mean and standard deviation (SD) and median and inter-quartile range (IQR) at baseline and at the 10-year follow-up in Table 7. Changes with small effect sizes implying worse HRQL at follow-up were found in the SIP Total and in the SIP Physical dimension but not in the SIP Psychosocial dimension. Changes implying worse HRQL at follow-up were found in the SIP categories Body care/movement, and Social interaction and a tendency for worse HRQL was found for the category Eating. The change in the category Emotional behavior tended to imply better HRQL at follow-up.

Table 7. Total score, dimensions and categories of the Sickness Impact Profile with means and standard deviations (SD) and median and inter-quartile range (IQR) in people with MS at baseline and at the 10-year follow-up, and p-values for changes from baseline to follow-up, and effect sizes; n =116

Sickness Impact Profile	Mean (SD)		Median (IQR)		p-value
	Baseline	Follow-up	Baseline	Follow-up	(Effect size)
SIP Total	19 (12)	22(13)	20 (10–28)	23 (11–33)	0.001 (0.25)
SIP Dimensions					
Physical	21(15)	26(18)	20 (7–34)	25 (11–39)	0.000 (0.33)
Psychosocial	14 (12)	15(13)	11 (6–21)	12 (5–21)	0.398 (0.08)
SIP Categories					
Sleep and rest			22 (10–35)	22 (10–34)	0.461
Emotional behavior			10 (0–25)	0 (0–23)	0.072
Body care/movement			16 (4–35)	24 (8–47)	0.000
Home management			29 (0–56)	41 (10–68)	0.108
Mobility			11 (0–24)	13 (0–25)	0.246
Social interaction			9 (0–17)	9 (3–20)	0.042
Ambulation			31 (12–40)	34 (23–40)	0.310
Alertness behavior			10 (2–30)	13 (0–39)	1.000
Communication			9 (0–20)	9 (0–21)	0.253
Work			25 (2–70)	24 (0–70)	0.815
Recreation/pastime			30 (19–46)	28 (10–48)	0.920
Eating			0 (0–5)	0 (0–11)	0.059

5.3.1.2 The EuroQol-5D

Regarding the EQ-5D Index a change with a small effect size (0.29) from baseline (mean 0.66 and SD 0.26) to the 10-year follow-up (mean 0.59 and SD 0.30) was found. There was no change from baseline (mean 64, SD 22) to the 10-year follow-up (mean 66 SD, 22) in HRQL as measured with the EQ VAS.

5.3.2 Predictors of changes in health related quality of life

Results from the final mixed model ANOVAs with REML for the SIP Total and the EQ VAS respectively, which included the disease-specific variables as independent variables, revealed that EDSS at baseline was the only significant variable for predicting a change in HRQL. A higher EDSS at baseline predicted a worse HRQL regarding both the SIP Total and the EQ VAS. In the final model for the EQ VAS, the independent variable "use of immunomodulatory treatment" indicated, but not significantly (p value=0.052), that the use of immunomodulatory treatment at baseline predicted a worse HRQL.

The final mixed model ANOVAs with REML for the SIP Total and the EQ VAS are presented in Table 8 and Table 9 respectively. A total of 99 PwMS were included in the analyses. The effects on HRQL as measured with the SIP Total revealed that EDSS Severe and EDSS Moderate as well as cognitive impairment at baseline predicted worse HRQL at the 10-year follow-up, depressive symptoms at baseline tended to predict worse HRQL (p value=0.062). The effects on HRQL as measured with the EQ VAS revealed that weak coping capacity and depressive symptoms at baseline predicted a worse HRQL, cognitive impairment at baseline tended to predict worse HRQL (p value=0.068). No interactions between time and the independent variables or between coping capacity and mood were seen in either model. The multiple linear regression analyses revealed that the adjusted R^2 was 0.378 for the SIP Total and 0.267 for the EQ VAS.

Table 8. Estimates of effects described as change in points of the independent variables and the time factor (0 and 10 year) on the Sickness Impact Profile Total with 95% confidence intervals, standard errors and p values, for the model with best fit, n=99

Independent variable	Variable categorization	Estimate[1] (95% confidence interval)	Standard error	p-value
Age	Age ≥ 51 years Age < 51 years	2.4 (-1.4 to 6.2) reference	1.9	0.220
Sex	Male Female	1.3 (-2.5 to 5.0) reference	1.9	0.504
Coping capacity	Weak Moderate or Strong	4.6 (-0.8 to 9.9) reference	2.7	0.094
Education	Ground level	1.1 (-3.1 to 5.3)	2.1	0.604

	High School or University	reference		
MS disability	EDSS Severe	12.4 (8.3 to 16.4)	2.0	0.000
	EDSS Moderate	6.5 (1.7 to 11.3)	2.4	0.008
	EDSS Mild	reference		
Depression	Depressive symptoms	6.3 (-0.3 to 13.0)	3.4	0.062
	No depressive symptoms	reference		
Cognition	Cognitive impairment	7.4 (0.6 to 14.1)	2.7	0.033
	No cognitive impairment	reference		
Time point	Follow-up	2.3 (-2.3 to 7.0)	2.3	0.315
	Baseline	reference		

[1]A positive estimate implies worse health-related quality of life.

Table 9. Estimates of effects described as change in points of the independent variables and the time factor (0 and 10 year) on the EQ Visual Analogue Scale with 95% confidence intervals, standard errors and p values, for the model with best fit, n=99

Independent variable	Variable categorization	Estimate[1] (95% Confidence interval)	Standard error	p-value
Age	Age ≥ 51 years	-1.0 (-7.7 to 5.8)	3.4	0.778
	Age < 51 years	reference		
Sex	Male	-4.9 (-11.6 to 1.8)	3.4	0.148
	Female	reference		
Coping capacity	Weak	-15.6 (-24.9 to -6.2)	4.7	0.001
	Moderate or Strong	reference		
Education	Ground level	3.7 (-3.7 to 11.1)	3.7	0.326
	High school or University	reference		
MS disability	EDSS Severe	-5.9 (-13.1 to 1.3)	3.6	0.107
	EDSS Moderate	-1.3 (-9.8 to 7.2)	4.3	0.765
	EDSS Mild	reference		
Depression	Depressive symptoms	-14.2 (-22.5 to -5.9)	4.2	0.001
	No depressive symptoms	reference		
Cognition	Cognitive impairment	-5.6 (-11.7 to 0.4)	3.1	0.068
	No cognitive impairment	reference		

Time point	Follow-up Baseline	3.3 (-1.3 to 7.9) reference	2.3	0.156

[1]A negative estimate implies worse health-related quality of life.

5.4 STUDY III

5.4.1 Primary care

A total of 23 379 contacts were registered for primary care during the 10-year study period. Nurses composed the largest proportion of all use in primary care. Number and proportion of users of primary care distributed by health care profession and mean (sd), median (IQR) and range of contacts is presented in Table 10. Almost all PwMS had been in contact with physicians and nurses during the 10-year study period.

Table 10.Use of primary care in people with MS during the 10-year period distributed by health care profession: number and proportion of users (%), mean (sd), median (IQR) and range of contacts, n=121.

Profession	Users, n (%)	Mean (sd)	Median (IQR)	Range
Total	121 (100)	192 (297)	91 (33-210)	1-1884
Physician	117 (97)	39 (52)	26 (10-43)	1-299
Nurse	113 (93)	91 (213)	20 (5-93)	1-1428
Occupational therapist	73 (60)	30 (30)	21 (7-43)	1-140
Physiotherapist	61 (53)	62 (117)	17 (3-85)	1-789
Nurse aid	24 (20)	37 (139)	4 (1-15)	1-689
Orthoptist	15 (12)	12 (11)	11 (2-18)	1-43
Welfare officer	12 (10)	6 (5)	4 (2-11)	1-16
Dietician	10 (8)	4 (4)	2 (1-7)	1-14
Psychologist	7 (6)	10 (7)	10 (4-14)	2-23
Podiatrist	7 (6)	16 (13)	12 (6-27)	1-40
Other[1]	15 (12)	6 (8)	2 (2-9)	2-25

[1]Includes professions where less than 5% of the people with MS had been in contact with

5.4.2 Hospital outpatient care

A total of 12 706 contacts were registered for hospital outpatient care during the 10-year study period. Neurology Departments and Rehabilitation Departments composed two thirds of all use of hospital outpatient care. Number and proportion of users of hospital outpatient care distributed by department and mean (sd), median (IQR) and range of contacts is presented in Table 11. Almost all PwMS had been in contact with Neurology Departments.

Table 11. Use of hospital outpatient care in people with MS during the 10-year period distributed by department: number and proportion of users, mean (sd), median (IQR) and range of contacts, n=121.

Department	Users, n (%)	Mean (sd)	Median (IQR)	Range
Total	120 (99)	106 (86)	72 (47-149)	9-543
Neurology	117 (97)	39 (31)	30 (16-50)	1-160
Medical service and radiology	103 (85)	5 (4)	4 (2-6)	1-23
Rehabilitation	92 (76)	42 (66)	18 (5-42)	1-350
Emergency	83 (69)	5 (6)	3 (1-7)	1-34
Urology	67 (55)	13 (16)	7 (4-17)	2-59
Ophthalmology	65 (54)	4 (4)	3 (1-6)	1-15
Obstetrics and gynecology	63 (52)	5 (5)	4 (1-6)	1-23
Surgery	61 (50)	7 (14)	3 (1-6)	1-79
Medicine	56 (46)	5 (7)	3 (1-6)	1-40
Orthopedics	50 (41)	4 (5)	2 (1-4)	1-30
Ear, nose and throat	30 (25)	2 (2)	2 (1-3)	1-9
Dermatology	21 (17)	2 (1)	1 (1-3)	1-4
Oncology	19 (16)	13 (17)	5 (2-23)	1-56
Geriatrics	17 (14)	5 (10)	2 (1-4)	1-41
Infection	13 (11)	5 (8)	1 (1-6)	1-30
Gastroenterology	11 (9)	7 (12)	2 (1-9)	1-33
Psychiatry	10 (8)	11 (19)	2 (1-31)	1-40
Endocrinology	8 (7)	3 (3)	2 (1-3)	1-10
Other[1]	56 (46)	14 (17)	7 (2-22)	1-71

[1]Includes departments where less than 5% of the PwMS had been in contact with

5.4.3 Hospital inpatient care

A total of 4108 days were registered for hospital inpatient care during the 10-year study period. Rehabilitation Departments composed one third of all inpatient care, followed by Neurology Departments which composed almost one third of all inpatient care. Number and proportion of users of hospital inpatient care distributed department and mean (sd), median (IQR) and range of days is presented in Table 12.Three quarters of all PwMS had been hospitalized at some point during the study period.

Table 12. Use of inpatient care in people with MS during the 10-year period distributed by department: number and proportion of users, mean (sd), median (IQR) and range of inpatient days, n=121.

Department	Users, n (%)	Mean (sd)	Median (IQR)	Range
Total	93 (77)	30 (47)	12 (4-37)	1-302
Neurology	39 (32)	23 (33)	12 (5-25)	1-167
Rehabilitation	38 (31)	38 (41)	26 (20-39)	2-222
Medicine	31 (26)	11 (12)	6 (3-16)	1-49
Surgery	30 (25)	12 (23)	5 (3-14)	1-132
Urology	16 (13)	21 (32)	6 (2-33)	1-120
Orthopedic	15 (12)	7 (8)	5 (2-8)	1-35
Infection	13 (11)	13 (19)	7 (4-15)	1-71
Geriatrics	10 (8)	17 (10)	14 (10-26)	6-37
Obstetrics and gynecology	6 (5)	7 (6)	6 (4-10)	1-18
Other inpatient care[1]	11 (9)	42 (82)	7 (4-98)	2-189

[1]Includes departments where less than 5% of the people with MS had been in contact with

5.4.4 Predictors of use of care

For total outpatient care, 65% of the contacts were registered in primary care and 35% were registered in hospital outpatient care. The final multivariable regression analysis for the use of total outpatient care revealed that a lower coping capacity, use of immunomodulatory treatment, limitation in manual dexterity, inability to walk, and limitation in ADL at baseline and a progress in EDSS, predicted a higher use of total outpatient care (Table 13). The adjusted coefficient of determination for the final multivariable linear regression model was 0.340.

Table 13. The final multivariable linear regression model for the predictive value of the independent variables at baseline, and progress in MS disability, on the use of total outpatient care during the 10-year period in people with MS (n=120[1]).

Independent variable	Categorisation of the independent variable	B	95% CI	Beta	p value
Coping capacity		-1.30	-2.74 to 0.20	0.15	0.08
Immunomodula-tory treatment	No	-41.76	-98.38 to -1.31	0.17	0.04
	Yes	reference			
Manual dexterity	Impaired	43.33	-4.29 to 114.26	0.18	0.08
	Not impaired	reference			
Walking	Cannot walk	105.01	23.86 to	0.26	0.01
	Walk without aid	reference	239.06		
Instrumental activities of daily living	Limitation	108.55	36.34 to	0.36	0.001
	No limitation	reference	218.67		
Progress in MS disability	>1 point change	48.59	5.76 to 108.76	0.20	0.02
	≤1 point change	reference			

[1]One person had no contacts with hospital outpatient care and was excluded from the multivariable regression analysis

The final multivariable regression analysis for the use of inpatient hospital care revealed that a weak coping capacity, limitation in manual dexterity and in personal ADL at baseline and a progress in EDSS predicted a higher use of inpatient care (Table 14). The adjusted coefficient of determination for the final multivariable model was 0.280.

Table 14. The final multivariable linear regression model for the predictive value of the independent variables at baseline, and progress in MS disability, on the use of inpatient care during the 10-year period in people with MS (n=121).

Independent variable	Categorisation of the independent variable	B	95% CI	Beta	p value
Coping capacity	Weak	167.51	12.64 to 535.18	0.19	0.03
	Moderate/strong	reference			
Manual dexterity	Impaired	233.01	82.58 to 507.30	0.36	<0.001
	Not impaired	reference			
Personal activities of daily living	Limitation	126.60	20.80 to 324.61	0.24	0.01
	No limitation	reference			
Progress in MS disability	>1 point change	145.22	39.38 to 331.89	0.27	0.002
	≤1 point change	reference			

5.4.5 Patient satisfaction with care

Overall, the proportions of PwMS satisfied with different dimensions of care were stable over time although the proportion of PwMS who were not satisfied with the accessibility to rehabilitation periods; the accessibility to psychosocial support and advice/support of social insurance/work rehabilitation; the availability of physicians; and the proportion who had participated in planning care ranged between 34-66% at both baseline and at the follow-up. There was a significant increase in the proportion of PwMS satisfied with: the accessibility of rehabilitation periods and home help service/personal assistance; the availability of nurses; and the efficacy of hospital outpatient care. No decrease in satisfaction with care over time was seen.

There was no difference in the use of care among PwMS satisfied compared to PwMS not satisfied with the efficacy/outcome of primary care (p=0.08), hospital outpatient care (p=0.99), hospital inpatient care (p=0.49) or inpatient rehabilitation (p=0.40).

5.5 STUDY IV

5.5.1 Recruitment, inclusion and follow-up

Recruitment of PwMS to the pilot study was conducted between June 2011 and January 2012. Three nurses and two neurologists at the MS-centre participated in the recruitment process by identifying PwMS for the screening process. It was found that the clinical practices of the therapists were not able to accommodate wheelchairs and PwMS with an EDSS $\geq$ 7.5 could therefore not be included. Twentyone PwMS were screened for inclusion. Of these, 15 PwMS met the inclusion criteria and were included. Of the 15 PwMS included, nine completed 15-20 sessions of face-to-face CBT and six PwMS discontinued the intervention. Of the six PwMS who discontinued the intervention, three were lost to follow-up.

5.5.2 Sample characteristics

Personal- and disease-specific characteristics of the 15 PwMS included in the study as well as of the completers and non-completers of intervention at inclusion are presented in Table 15. Twelve of the 15 included patients were women, mean age at inclusion was 38 years (SD 7), and 11 PwMS were working full- or part-time. For twelve of the PwMS the EDSS was assessed as 3.5 or lower. Thirteen PwMS used immunomodulatory treatment and one PwMS used antidepressant medical treatment. Five out of nine completers and one out of six non-completers had university education. The mean time since diagnosis was three years for completers and eight years for non-completers.

Table 15. Personal- and disease-specific characteristics presented for all people with MS included, as well as for completers and non-completers of face-to-face cognitive behavioural therapy, respectively.

Variable at inclusion	All, n=15	Completers, n=9	Non-completers, n=6
Female, n	12	8	4
Mean age, years (sd)	38 (7)	39 (7)	38 (9)
Living with a partner, n	10	6	4
Living with children, n	9	7	2
Level of education, n			
Primary/Lower secondary level	1	0	1
High school	8	4	4
University	6	5	1
Working full- or part- time, n	11	7	4
Sick-leave full- or part- time, n	6	3	3
Coping capacity, n			
Moderate to strong	7	4	3
Time since diagnosis			
Mean (sd) in years	5 (5)	3 (4)	8 (6)

Type of MS, n			
Relapsing-remitting	12	7	5
Secondary progressive	2	1	1
Primary progressive	1	1	0
Disease severity, n			
EDSS Mild	12	7	5
EDSS Moderate	2	2	0
EDSS Severe	1	0	1
Immunomodulatory treatment	13	9	6
Antidepressant drug, n	1	0	1

5.5.3 Feasibility outcomes

The average recruitment rate was two PwMS/month, the completion rate was 60%. Of those who did not fulfil the CBT intervention, three had participated in equal to or more than two sessions of CBT.

The average number of CBT sessions was 12/PwMS (range 2-20 sessions) including enrolment sessions, and there was a mean of 3 late cancellations/PwMS. The average length of the intervention was 25 weeks. The intensity of the intervention varied with an average intensity of 0.5 session/week.

The screening and the data collection procedure at the Department of Neurology, Karolinska University Hospital, Huddinge were found to be feasible. No adverse events were reported. No instrument demonstrated floor effects although four instruments demonstrated ceiling effects: for the LMCA 10 out of 15 scored the maximum score at inclusion; for the BI 13 out of 15; for the Katz P-ADL Index 15 out of 15; for Katz I-ADL Index 11 out of 15 scored maximum scores at inclusion

5.5.4 Clinical outcomes

Mean (sd) and 95% confidence intervals of outcomes of measurements of depressive symptoms, anxiety and HRQL at inclusion, three weeks follow-up and three months follow-up are presented according to ITT and for completers respectively, in Table 16. The ITT analyses showed a decrease of the depressive symptoms according to the BDI-II from a mean of 17 at inclusion to a mean of nine at three weeks follow-up and eight at three months follow-up. The completer analyses demonstrated quite similar results as the ITT analyses regarding all measurements used.

Table 16. Mean (sd), and 95% confidence interval (CI) of outcomes of the Beck Depression Inventory-II (BDI-II), the Hospital Anxiety and Depression Scale (HADS), the Multiple Sclerosis Impact Scale 29 (MSIS-29), EQ VAS and the EQ Index at inclusion, three weeks follow-up and three months follow-up, presented for intention-to-treat analyses (ITT) and for completers analyses respectively.

	Inclusion		3-weeks follow-up		3-months follow-up	
Test or questionnaire	ITT, n=15	Completers, n=9	ITT, n=15	Completers, n=9	ITT, n=15	Completers, n=9
BDI-II						
Mean (sd); 95% CI	17 (3); 15-18	17 (2); 15-19	9 (5); 6-12	7 (4); 4-11	8 (6); 5-11	7 (4); 4-11
MSIS-29						
Psychological component						
Mean (sd); 95% CI	28 (5); 25-31	28 (6); 23-33	17 (4); 15-23	17 (4); 13-20	15 (4); 14-22	15 (5); 12-19
Physical component						
Mean (sd); 95% CI	43 (15); 34-51	42 (15); 30-53	31 (11); 28- 44	31 (11); 23-39	31 (11); 28-44	33 (12); 23-41
EuroQol 5D						
EQ VAS						
Mean (sd); 95% CI	60 (19); 50-71	57 (22); 40-74	71 (15); 62-80	73 (16); 61-86	71 (16); 63-80	73 (15); 61-84
EQ Index						
Mean (sd); 95% CI	0.6 (0.2); 0.5-0.7	0.6 (0.2); 0.5-0.8	0.7 (0.2); 0.7-0.8	0.8 (0.1); 0.7-0.9	0.8 (0.2); 0.7-0.8	0.8 (0.2); 0.7-0.9

5.5.5 Estimated sample size calculation

The sample size estimates per group are summarized in Table 17. With a sample size of 45 per group, a two group t-test with a significance level of 0.05 and a standard deviation of 5 will have 80% power to detect a difference in means of three points.

Table 17. Sample size estimates per group with 80% power and differences in points of the Beck Depression Inventory-II (BDI-II) in a two group t-test with equal means with a significance level of 0.05

Mean differences in points of the BDI-II	Effect size	Sample size per group (n)	Total sample size (attrition adjusted)
5	1.00	17	48
4	0.80	26	73
3	0.60	45	126
2	0.40	100	280

6 DISCUSSION

6.1 MAIN FINDINGS

There was no change in occurrence of PwMS with cognitive impairment, depressive symptoms or restrictions in social/lifestyle activities from baseline to the 10-year follow-up. There was an increase in occurrence of PwMS with limitation in manual dexterity, in walking ability and in ADL over time. The psychosocial dimension of HRQL was stable over time while the physical dimension decreased implying a worse HRQL, however only to a limited extent. The use of care over time was extensive and included primary care, hospital outpatient and inpatient care and involved many different departments. The EDSS was an important variable to predict disability at the 10-year follow-up. Depressive symptoms at baseline was an important variable to predict the outcome of a lower HRQL at the 10-year follow-up and an increased mortality rate. Low coping capacity at baseline was an important variable to predict the outcome of depressive symptoms, a lower HRQL, and a higher use of care. Even if patient satisfaction with care was quite stable over time, our findings demonstrate that there is room for improvements. Overall, the methods and measurements used in the pilot feasibility study of face-to-face CBT were found to be feasible.

6.1.2 Changes in disability and predictors of disability and mortality

6.1.2.1 Changes in occurrence of disability

That the occurrence of depressive symptoms was stable over time needs further investigation on an individual level but is in line with previous findings (31, 166). Depressive symptoms in PwMS have been found to be undertreated pharmacologically (37) and even though there was an increased use of antidepressant drugs, the increase was not among those with depressive symptoms. The increased use of antidepressant drugs could instead be explained by an increased treatment of, e.g., neurogenic pain.

Considering the progressive nature of MS, it was a somewhat unexpected finding demonstrating that there were no changes in occurrence of PwMS with cognitive impairment or restrictions in social/lifestyle activities from baseline to the 10-year follow-up. Previous research have demonstrated that cognitive preservation in PwMS may be intact over a short period of time, while cognitive deterioration tends to progress over time (49, 55, 56). Although the occurrence of PwMS categorised as having a cognitive impairment did not change over time, a significant decrease in the raw score of the SDMT was seen. A possible explanation for this result can be that the raw score of the SDMT was compared to age-related norms and the categorisation of impairment was adjusted to age. Since the outcome results of the SDMT was dichotomized, we do not know if those PwMS already categorised with impaired cognition worsened in their cognitive function over time.

That the occurrence of restrictions in social/lifestyle activities was stable over time might also be an effect of a categorization that was adjusted to age (and gender) related norms (150). It could also be explained by an adaptation process to the consequences of living with MS over

time, facilitated by contextual factors such as a moderate or strong SOC and/or facilitating environmental variables such as the use of care services which enabled their participation in society despite increased disability (19). However, a qualitative study exploring the experience of living with MS in the severe stages of the diseases found that from the perspective of the PwMS, when EDSS increases, it can be hard or impossible to find new and meaningful activities (18).

More expectedly was the increase in occurrence of PwMS with limitation in manual dexterity, walking ability and limitation in ADL. Considering how important it is to manage new digital technology such as computers, smart-phones and tablets to participation in our society, it is possible that manual dexterity plays an even greater role today compared to baseline. This point highlights the importance for manual dexterity to also be thoroughly assessed and that studies on the effect of specific interventions that aim to sustain/improve manual dexterity should be required. There were significant changes in occurrence of PwMS with limitation in both P-ADL and I-ADL, but the change in I-ADL was higher. This has been reported previously in a cross-sectional study of PwMS (167) and indicates the importance of measuring both P-ADL and I-ADL in order to capture the needs that a PwMS requires to manage daily life.

6.1.2.2 Predictors of changes in occurrence of disability

Sex and EDSS at baseline did not predict the outcome of depressive symptoms in our study (31). In the general population, female sex is a risk factor for depressive symptoms (168). Differences in results might be attributional to differences in aetiology between depressive symptoms in PwMS compared to the aetiology of depressive symptoms in the general population. The aetiology of the depressive symptoms in PwMS needs further investigation since the treatment method might differ depending of the cause. That the EDSS at baseline was not an important variable to predict a change in occurrence of depressive symptoms over time is in accordance with results from other studies (31, 166) and suggests that depressive symptoms occur regardless of disease severity. A weak SOC was the only important variable to predict an increase in occurrence of PwMS with depressive symptoms. The discriminative validity of the SOC scale in relation to measures of depression has though been questioned (169, 170) and biological parameters of depression such as saliva cortisol have been found to correlate in the same way to SOC (170). However, in the GEE analysis, multicollinearity between the SOC and the BDI were controlled for but was not found.

Despite the criticism against the EDSS regarding validity and reliability (123, 124), it was found to predict an increase in occurrence in several areas of disability. This information is useful when planning for the overall coming care needs for the individual.

Time was not a significant independent variable or interacted with any other independent variable in the outcomes of cognitive impairment or depressive symptoms, suggesting that these impairments occurred early during the MS trajectory and that time did not change the occurrence of PwMS with disability in these outcomes.

6.1.2.3 Predictors of mortality

Depressive symptoms at baseline was one predictor for an increased mortality rate over the 10-year period. Although this result needs to be confirmed in larger populations-based studies, it highlights that care professionals need to be aware of the psychological aspects of the disease.

6.1.3 Changes in HRQL and predictors of a change in HRQL

6.1.3.1 Changes in HRQL

Our results of a worsened HRQL according to the SIP Total, the SIP Physical dimension and the EQ-5D Index over time, could be expected considering the increased EDSS over time, however, the effect sizes of these changes were small.

More surprisingly, however encouraging, were our results demonstrating a stable HRQL according to the SIP Psychosocial dimension and the EQ VAS. This finding is consistent with previous findings in short-term longitudinal studies of HRQL in PwMS (100-102), but seems to apply even in a long-term perspective (10 years). However, there is a possibility for individual differences over time (100). Unexpected findings in HRQL in PwMS have been explained by the theory of response-shift (100, 102) which refers to changes in internal standards, in values or in the conceptualisation of HRQL, catalysed by health-state changes (171). The underlying process of response-shift has been described as a way to cope with chronic illness (172, 173) and indeed, weak coping capacity was a predictor for worse HRQL according to the single global question (EQ VAS). There are studies demonstrating that the type of coping strategy is important, at least regarding the psychosocial dimension of HRQL, which implies that educating PwMS in coping strategies is a way to increase HRQL (174, 175) in this group.

6.1.3.2 Predictors of a change in HRQL

EDSS (99), depressive symptoms (102, 176, 177) and cognitive impairment (177) have been found to predict worse HRQL in PwMS in a short-term perspective, findings that also seems to apply to a 10-year perspective. In the present study, the EDSS predicted worse HRQL according to the health profile, but according to the single global question, the EDSS was not that important for predicting HRQL. This suggests that the EDSS is not that important in the concept of HRQL according to the PwMS themselves Since depression is a treatable condition (115), there is a potential to improve HRQL in PwMS by identifying and initiating evidence-based treatment for depressive symptoms (115).

The prediction models explained almost 40% of the variance in HRQL according to the health profile (SIP Total) and almost 30% according to the single global question (EQ VAS). Even though the single global question might capture important determinants of HRQL, results from a visual analogue scale alone are difficult to interpret in clinic (178) because such results do not substantiate the rating of the respondent.

6.1.3.3 HRQL in those PwMS who died during the 10-year follow-up

HRQL according to the health profile (SIP Total) differed significantly at baseline between those PwMS who died during the 10-year period and those PwMS who were alive at the 10-year follow-up, but not according to the single global question (EQ VAS). Those who died were also significantly older and had a higher EDSS at baseline compared to those who were alive. Previous studies have demonstrated that HRQL is an important predictor for survival with cancer and heart failure (179-181). To my knowledge, no such studies have yet been conducted with PwMS. Further studies are needed to explore the associations between HRQL and mortality rates of PwMS.

6.1.4 Use of care, predictors for use of care and patient satisfaction with care

6.1.4.1 Use of care

There was an extensive use of care over time, including primary care, hospital outpatient and inpatient care with many different departments involved. Primary care accounted for the majority of all outpatient contacts. However, the use of care was non-normally distributed in the study cohort indicating that there was a smaller proportion of PwMS using a majority of the care. For those PwMS who use care extensively, coordination between care providers might be a challenge. This challenge must be addressed since successful coordination of care has a potential to increase health outcomes and reduce the risk for duplicative or contra-indicated care (182).

Compared to another study exploring the use of care in PwMS in Sweden (183) our study reported a lower use of total outpatient care and number of inpatient days. In an international perspective there are studies reporting both a lower and a higher amount of visits to neurologists (184, 185) compared to our study, and a higher use of inpatient days at the Neurology Departments (185). Differences in results might be attributable to differences in study sample, types of data collection, and length of follow-up. These differences as well as differences in how care services are organised between countries can make comparisons of results a challenge.

Considering that MS is a neurologic and progressive disease, it was surprising to find that the Neurology Departments did not account for more than about one-third of all hospital outpatient care. Compared to other European countries the number of neurologist per thousand inhabitants in Sweden is low (186). This could explain the relatively low use of outpatient care at the Neurology Departments.

6.1.4.2 Predictors for use of care

The EDSS at baseline did not predict the outcome of use of care over time and this was a somewhat surprising result, which differs from that of another study (105). Rather, a progress over time in the EDSS predicted an increased use of care implying that it is a *change* in disability that drives the use of care. Limitation in manual dexterity was an important variable

to predict a higher use of both hospital outpatient and inpatient care. It is possible that manual dexterity is an even more essential function today compared to 10 years ago considering the need to manage a computer, smart-phone or tablet device has almost become a prerequisite in order to participate in our society. A limitation in manual dexterity could therefore restrict participation in society and induce a need for care i.e. rehabilitation or testing of facilitating environmental factors. It is interesting that low coping capacity predicted a an increased use of hospital inpatient care since it may point to the importance of self-management programs as an essential part of MS care, at least for those PwMS demonstrating a low coping capacity. Indeed, self-management programs has emerged as an important part of the care for people with chronic diseases, including MS, aiming to learn how to managing aspects of living with for example MS, even if further studies is warranted (187). In PwMS, self-management programmes have demonstrated positive effects on managing for example fatigue (188), to increase adherence to immunomodulatory treatment (189) and to decrease mild anxiety/depressive symptoms (190). Potentially, self-management programs could lead to a decrease in the need and use of care.

The prediction models of the use of care explained about one-third of the variance of the use of outpatient care and one-quarter of the use of inpatient care. Even though other variables not included in the models contribute to the variance of the use of care, the similarity between the models strengthens our results.

6.1.4.3 Patient satisfaction with care

Even though the high prevalence of depressive symptoms for PwMS is well-known (36) and despite the increasing number of studies reporting encouraging results of the effectiveness of different psychological treatment methods in reducing the depressive symptoms of PwMS (119), the satisfaction with the accessibility to psychosocial support/counselling was low over time. The high proportion of PwMS reporting that they had not participated in planning their care is noteworthy since a patient-provider partnership has been found to be successful in i.e. improving health outcomes (182). The proportion of PwMS satisfied with the accessibility to rehabilitation periods increased over time, however about one third of the PwMS was still not satisfied. This finding is important since rehabilitation interventions is most important do decrease the impact of the disease on impairment, activity limitation and participation restriction.

6.1.5 Feasibility of face-to face CBT

Even though all PwMS meeting the criteria for depressive symptoms were successfully included, the recruitment rate of patients to the study was low. We therefore recommend a screening process for a future effectiveness study of comparative methods of face-to-face CBT. A screening process has limitations including poorer external validity and significantly lower effect sizes (191), however, since PwMS rarely seek treatment for depression a screening process would be useful (192).

One possible limitation was that no psychiatric confirmed diagnosis of depression was used for inclusion. By including PwMS with sub-threshold depressive symptoms there is a risk of including PwMS with false-positive answers, however, by increasing the cut-off point to 13 at the BDI-II, approximately 30% of the PwMS with depressive symptoms might be missed (193). To ensure the accuracy of the depressive symptoms we recommend that a certified psychologist should be engaged in the analyses of the BDI-II, and that PwMS with sub-threshold to moderate depressive symptoms should be included but that stability in the depressive symptoms should be ensured by two assessments, at screening and before entering treatment.

It was challenging recruiting therapists since there is a lack of the recommended competence in Stockholm County, however because of the challenges of treating people with chronic diseases it is important to recruit therapists with formal competence (115). The physical inaccessibility for wheelchair users at the clinical practices raises a concern about the equitability of psychosocial care regardless of physical functioning.

Even though no conclusions on the effects of treatment can be drawn from this pilot study, the differences in depressive symptoms according to both the BDI-II and the HADS and the improvement in HRQL according to the MSIS-29 and the EuroQol-5D should be noted. The possibility of modifying CBT to the needs of the patients might be greater with face-to-face CBT compared to internet- or telephone CBT and might be an important factor for decreasing the depressive symptoms. Also noteworthy is the high number of PwMS demonstrating anxiety symptoms at inclusion; therefore, possible changes in anxiety symptoms should be examined in an effectiveness study of comparative methods of CBT.

The ceiling effect noted in the BLMCA, BI and KE, implies that these instruments were not useful for this particular sample. If including PwMS with a disease severity over EDSS 7.0 then we recommend retaining these instruments. Considering that CBT aim to change thoughts and behaviours, which can take time, a follow-up time of three months might have been too short. We recommend that the follow-up time should be extended to one year.

Since this pilot study was conducted, two valuable articles on CBT as a treatment method to alleviate depressive symptoms in PwMS have been published (126, 194). These studies proposed that CBT might be an effective method for alleviating depressive symptoms in some subgroups in PwMS but that further knowledge is needed (126, 194) in order to identify those PwMS who would benefit from CBT as well as the long-term effects (194). Furthermore, that further research is needed in comparative non-pharmacological interventions including different approaches (126). With this in mind, we propose a main study including two treatment arms, one arm including traditional face-to-face CBT and the other including a shorter, low-intensity face-to-face CBT.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Selection bias

Selection bias could introduce a systematic error into a study if the probability of being selected to the study is related to the independent variables and the outcome (195). When using a population-based sample, such as in Study I, II and III in this thesis, the risk for selection bias is reduced compared to using a clinical-based cohort (the requirements of the population-based case ascertainment have been described previously (52)). However, 15% of those PwMS identified at baseline, declined to participate in the baseline study. In addition, at the 10-year follow-up, another 11 PwMS declined to participate and 32 PwMS had died. Those PwMS who died were older, had a higher EDSS and a lower HRQL at baseline compared to those who were alive at the 10-year follow-up.

6.2.2 Misclassification of the independent variables

Misclassification of the independent variables is also a systematic error that might occur in a study. This might lead to an underestimation of the association between the independent variable and the outcome and thereby result in a false negative finding (195). In Study I, II and III most of the independent variables were dichotomized or categorised and might therefore be subjected to misclassification. In Study I, II and III the independent variables under greatest risk for misclassification would be 'Age' and 'Time since diagnosis'. The cut-off for the independent variable 'Age' was the mean age in the cohort at inclusion and is not an established cut-off for "old age". The cut-off for 'Time since diagnoses' is based on the assumption that changes in MS disability occurs frequently during the first 10 years but is not an established cut-off. Through using norm data from reference groups regarding cut-offs for a low coping capacity (Study I, II and III), impaired cognition (Study II and III), limitation in manual dexterity (Study III) and restrictions in frequency of social/lifestyle activities (Study III), this might reduce the risk for misclassification.

6.2.3 Misclassification of outcome

Misclassification of outcomes can also introduce systematic errors into a study (195). In Study I, all outcome variables were dichotomized and are therefore at risk for misclassification. The use of established cut-offs using norm data from reference groups regarding cognitive impairment, impaired walking speed and restrictions in frequency of social/lifestyle activities and the use of recommended cut-offs for depressive symptoms might reduce the risk for misclassification.

6.2.4 Measurement error

Measurement errors might occur in a variety of ways and includes both the independent variables and the outcomes. Measurement errors include:

1. Instrumental errors, arising from an imprecis instrument, questionnaire limitations or an inaccurate diagnostic test.

2. Respondent errors, such as misunderstanding the question or faulty recall.
3. Observer errors, such as mistakes, imprecise procedures or a misunderstanding of procedures.
4. Data processing errors, including coding, programming and calculating mistakes (196).

To decrease the risk off instrumental errors, the majority of the instruments used were choosen because of their overall good psychometric properties, however, not all tests and questionnaires were validated or tested for reliability in a MS population. Some instruments demonstrated limitations and comprises the EDSS for which the validity and reliability has been questioned (123, 124), the SDMT since it does not capture all aspects of cognition which might lead to an underestimation of the occurrence of cognitive impairment. In addition, the low sensitivity of the MMSE to detect global cognitive impairment in PwMS (162) might lead to an underestimation of the proportion of PwMS with cognitive impairment. Considering that the FAI was constructed almost 30 years ago, it is possible that this instrument does not capture all the aspects of social/lifestyle activities of today. In Study II, generic instruments to assess HRQL were used. This might lead to that important issuses of HRQL specific for the PMS might not be captured.

In Study III, the conceptual framework of 'patient satisfaction' has been questioned. In addition to the framwork proposed by Ware, Carlin et al has proposed a framwork based on the assumption that the overall satisfaction with care is a function of the difference between the expected care and the actual experience: the greater the difference between the expected care and the actual experience, the lower reported patient satisfaction (197). However, there are studies demonstrating no or low association between patient satisfaction and the safety and outcome of care (198, 199). In a study including people with chronic diseases, comprising of ischemic heart disease, chronic obstructive pulmonary disease and diabetes it was found that patient satisfaction with care was more strongly associated with the self-reported ability to cope with the condition than with disease severity. This implies that patient education and self-management may lead to improved patient satisfaction with care (198). In addition, Carlin et al concluded in their study of people with chronic diseases that care providers who invest in improving their communication with patients will also receive higher levels of patient satisfaction, regardless of disease severity (197). Even though the concept of satisfaction with care is not yet fully distinguished, it does provide the patient perspective on aspects of care services and, in that sense, can be used to evaluate changes in or to improve care organisations and services.

By using face-to-face data collection in all the studies in this thesis, there is a risk that the observer influenced the respondent and thereby resulting in respondent error. However, the presence of the observer might also decrease the risk for respondent error since there was an opportunity to explain the questionnaires and to ensure that the questionnaires were filled in properly and by the right person. To decrese the risk for observer error the datacollection was performed in a standardised manner and the datacollectors were calibrated before the study.

The risk of data processing errors can be difficult to detect, so to ensure that these errors were as low as possible, all data in this thesis have been validated by two examiners.

6.2.5 Confounding variables

A confounding factor is a variable that is associated with both the independent variable and the outcome variable and is not a part of the causal chain between the independent variable under study and the outcome variable. In observational studies, the control of confounding variables will be a major concern (196). There are different statistical strategies to control for confounding variables, however these strategies were not applied in the regression models in Study I, II and II. Instead, the independent variables were selected based on empirical and or theoretical considerations, which could be more important than statistical strategies in choosing appropriate confounders (196).

6.2.6 Regression analyses

The aims of the regression models in Study I, II and III were not to derive the importance of a particular independent variable, but rather to explore the importance of various independent variables to predict the future value of the outcome variable. The independent variables included in the models were selected by empirical and/or theoretical considerations. A stepwise selection procedure was then used to create the final model. However, there is a major concern with the stepwise selection procedure in that it tends to overestimate the regression coefficient indicating that the performance of the model in predicting future values of the outcome will not be as good as we might expect (196). To reduce the risk of an overestimated regression coefficient the threshold for retaining an independent variable can be adjusted against a lower p value. This in turn might result in omitting an independent variable with an actual effect on the outcome. The risk for omitting an independent variable with an actual effect on the outcome is greater in Study I compared to in Study II and III since the p value was adjusted to a lower value in the regression analyses in Study I.

6.2.7 Generalizability

Generalizability or external validity refers to the extent to which the results can be generalised to other populations or situations (196). By using a population-based cohort as in Study I, II and III the generalizability increases compared to using a clinical-based cohort. However, the prevalence of MS in Sweden is higher today compared to about 10 years ago (15, 200) and possible differences in the male to female ration today compared to 10 years ago might affect the generalizability of the results. In addition, since the baseline data collection was performed (between September 1999 and September 2002) there has been a huge development not just regarding new and more effective immunomodulatory drugs but also in more advanced imaging techniques leading to a greater understanding of the disease and a possibility for an earlier diagnosis and thereby an earlier initiation of immunomodulatory treatment. There are several new and convincing studies which have demonstrated the positive impact of immunomodulatory treatment on MRI parameters (201-203) clinical outcomes such as relapse rate and disability progression (204-206) and HRQL

(207, 208). This is a welcomed development but challenge the generalizability of the results from Study I, II and III to new generations of PwMS. Hopefully, the new generations of PwMS will experience less impact on functioning and HRQ from the disease. However, since there is yet no cure for MS, one characteristic of the disease will still be a progressive increase in many areas of disability and an extensive need of different care services as demonstrated in Study I and III.

6.2.8 Methodological considerations in study IV

The methodological considerations regarding Study IV differs from those of Study I, II and III. One of the main methodological limitations in Study IV was the lack of predefined stop/go criteria, which would have facilitated the interpretation of the feasibility of an effectiveness study. The inclusion procedure attempted to imitate clinical praxis to initiate treatment for depressive symptoms but the lack of a psychiatric confirmed diagnosis of depression might be considered a limitation and a proposal to diminish this limitation is described. The estimated sample size calculation also has limitations. The small sample size might overestimate the clinical effect size (209) and difficulties in assessing a clinically important change of the BDI-II in MS-populations has previously been reported (210). These limitations are important to consider when estimating the total sample size for an effectiveness study of CBT.

6.3 STUDIES WITHIN THE ICF FRAMEWORK

When doing research about disability and health among PwMS it is important to include all components of the ICF structures since these components interacts with each other and produce different health outcomes. The comprehensive protocol used for data collection in all studies was constructed in order to include information from all components of the ICF structure in order to mirror the multifaceted aetiology of health in PwMS.

6.4 ETHICAL CONSIDERATIONS

For some PwMS, the time taken for data collection might have been experienced as too long and tiresome. However, the experience from the baseline data collection in Study I, II and III was that the PwMS appreciated the attention as well as the possibility to bring up issues not normally dealt with by care professionals. It is possible that for some PwMS, some of the tests and questionnaires conducted might have been experienced as discouraging or violating integrity. To diminish that risk, the PwMS were clearly informed of the possibility to decline participation. When needed, the data collector informed the PwMS about where to turn for professional support in different matters.

6.5 CONCLUSIONS AND CLINICAL IMPLICATIONS

Even though there is still much to learn about the pathophysiology of MS, the last decades have provided new technology and treatment options which improves the prognosis of living with MS. However, the results from our studies clearly demonstrate that the vast majority of the PwMS will face disability in many areas of functioning leading to impairment, limitations

in activity and participation restrictions during the MS trajectory. For a disease without cure, symptom management needs to be an essential part of the care of PwMS. The results also demonstrate that there is room for improvement regarding the organisation of the comprehensive care used by PwMS. The following conclusions could be useful to consider when to create the prerequisites for long-term sustainability, effective and equal health for PwMS:

6.5.5 Study I, II and III

- The stable proportion of PwMS with depressive symptoms over time urge an increased focus on mood disorders in PwMS and the initiation of evidence-based treatment when necessary
- The finding of increased occurrence of PwMS facing disability over time in many concurrent areas demands the use of multidisiplinary teams in order to meet all the needs of the PwMS
- The EDSS could be used as a tool to predict subsequent disability
- There is a potential to increase HRQL of PwMS by identifying those with depressive symptoms and/or cognitive impairment and initiate evidence-based treatment, as well as meeting the need for environmental facilitators aimned at reducing disability
- The comprehensive use of care by the PwMS offers challenges to care coordination which demands further investigation
- Implementation of person-centred care including self-management programmes, could be a strategy to increase efficacy/outcome of care

6.5.6 Study IV

- For an effectiveness study of CBT, a screening process for depressive symptoms and two comparative intervention arms including traditional face-to-face CBT and low-intensity face-to-face CBT is recommended. Primary outcomes should include the BDI-II and assessment of anxiety symptoms.

6.6 FUTURE STUDIES

Results from this thesis demonstrated that the proportion of PwMS with cognitive impairment and restrictions in frequency of social/lifestyle activities was stable over time (10 years). These results need to be confirmed using other validated instrument when considering that the use of SDMT might underestimate the proportion of PwMS with impairment and since the validity of the FAI might be questionable.

The proportion of PwMS with depressive symptoms was also stable over time. This finding represents an urgent need for studies that investigate the specific aetiology of depressive symptoms of PwMS. There is also a need for a continued focus on which subgroups of PwMS that would benefit from different treatment methods for the depressive symptoms i.e. different forms of psychological and/or medical treatment.

A low coping capacity was identified as an important predictor for the outcome of depressive symptoms, a lower psychosocial dimension of HRQL as well as a higher use if hospital inpatient care. This variable seems to be important when studying these outcomes and should therefore be included in future studies of these outcomes.

The use of care was studied in Stockholm County, an urban area of Sweden. To create equal care for PwMS in Sweden, there is a need for a longitudinal study investigating the use of care in rural areas of Sweden since differences in the organisation of care might lead to different uses of care. The results from this thesis demonstrated that the use of care was unequally distributed between the PwMS. Identification and further knowledge on this group of 'high-consumers' of care would be valuable since it is possible that this group has special needs regarding the need for example help in order to utilise self-management strategies, assitance with coordination of care etc.

Patient satisfaction with care is becoming an important tool for care providers and stakeholders to evaluate the outcomes of different care services (211). However, further studies of the underlying concept of satisfaction with care are needed since it has been questioned what the concept include and which outcomes it is supposed to measure.

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